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## Methodologic Concerns on the Reported Values for Assessing Permeability of the Blood-Brain Barrier in the Hippocampus

We read with great interest the article by Ivanidze et al<sup>1</sup> in the March issue of the *American Journal of Neuroradiol*.

In this article, the authors suggested a normative value for assessing the permeability of the blood-brain barrier (BBB) in the hippocampus, the volume transfer constant ( $K^{\text{trans}}$ ), which is potentially valuable to researchers and neuroradiologists.

We are concerned, however, about the methods used by the authors of this article and about the results presented.

First, the authors used the extended Tofts model to generate hippocampal  $K^{\text{trans}}$  values in their study. However, expert consensus is that the Patlak model is better than other models such as the extended Tofts model to measure very small changes in BBB permeability ( $K^{\text{trans}}$ ).<sup>2,3</sup> According to Barnes et al,<sup>2</sup> the highest contrast-to-noise ratio for  $K^{\text{trans}}$  was obtained when the analysis by the Patlak model was combined with long scan times (10–30 minutes), modest temporal resolution (<60 s/image), and long baseline scans (1–4 minutes). Therefore, the documented  $K^{\text{trans}}$  value of the hippocampus obtained using the extended Tofts model may not be as useful as expected.

Second, the authors did not provide the full details of the dynamic contrast-enhanced MR imaging (DCE-MR imaging) sequence used in their study. Recently, a consensus recommendation on the imaging of BBB permeability in small-vessel disease was published.<sup>3</sup> The recommendation would be applicable to all diseases with small changes in BBB permeability. It suggests that reporting of imaging results of BBB permeability should include full details of DCE- and T1-weighted MR imaging measurements, image preprocessing, selection of vessel input function, model fitting, formulas, generation of region and tissue mask, and post-processing and statistical analysis of data. Especially, one should document the following MR imaging acquisition parameters: the pulse sequence used for DCE- and T1-weighted MR imaging, flip angle mapping, field strength, inversion-/saturation-recovery delay, TR, TE, flip angle,  $k$ -space sampling scheme, acceleration technique, bandwidth, orientation, acquisition matrix, FOV, acquired spatial resolution, temporal resolution, and acquisition time and signal drift.<sup>3</sup> Among them, the flip angle and acquisition

time are very important for accurate calculation of  $K^{\text{trans}}$  values in the brain.<sup>4,5</sup>

Third, the spatial resolution and section thickness of the DCE-MR imaging sequence used were not optimal. Measurement of BBB leakage is essentially the leakage of fluid through capillaries, and not through medium- and small-sized vessels. Thus, the presence of a marginally large vascular component within the voxel might contaminate the results. As seen in Fig 1 of Ivanidze et al,<sup>1</sup> the ROI drawn on axial MR images with a thick section (5 mm in this study) almost always includes the hippocampal artery and its branches. This might inevitably lead to abnormally high  $K^{\text{trans}}$  values of the voxels. Furthermore, contamination by CSF could alter the value of BBB permeability of the voxels. ROIs of the hippocampus in the study of Ivanidze et al covered the choroidal fissure as well as the hippocampus. Therefore, an unknown amount of CSF, contained within the choroidal fissure, could have contributed to the measurement of BBB permeability; moreover, in their case, the signal contributed by the CSF did not appear to be removed accurately by the analysis software.

Fourth, we suspect that some systemic error might have contributed to the unusually high  $K^{\text{trans}}$  values reported with the Olea software (Olea Medical, La Ciotat, France). The reported  $K^{\text{trans}}$  values in the study deviate considerably from those reported in the recent literature, which is approximately 0.001 minutes<sup>-1</sup> in an animal study<sup>6</sup> and  $<2.5 \times 10^{-3} \times \text{minutes}^{-1}$  (0.0025 minutes<sup>-1</sup>) in human subjects.<sup>7</sup>

In our hospital, we evaluated and compared the results of the  $K^{\text{trans}}$  map obtained by DCE-MR imaging of 1 healthy subject, using both the nordicICE (NordicNeuroLab, Bergen, Norway) and Olea software. We chose the same mathematic model (extended Tofts model) used in the study of Ivanidze et al.<sup>1</sup> Most interesting, we found that the Olea-derived  $K^{\text{trans}}$  value was 100 times larger than that derived by the nordicICE software. We compared the 2 software products using the exact same options (without selecting an additional option).

Finally, the unit for the  $K^{\text{trans}}$  reported might be confusing to some readers. The commonly used unit for expressing the  $K^{\text{trans}}$  value is minutes<sup>-1</sup>.<sup>4</sup> The authors have stated that  $K^{\text{trans}}$  is expressed in milliliters/minute/100 mg.<sup>1</sup> In the literature, the unit


of  $K^{\text{trans}}$  is expressed in milliliters/minute/milliliter or milliliters/minute/ $\text{g}^4$  or milliliters/minute/100 mL.<sup>8</sup> The unit volume of tissue is expressed per 100 mL rather than in grams because imaging devices measuring cross-sectional areas provide the data of tissue volume.  $K^{\text{trans}}$  is a volume transfer constant between the blood plasma and extravascular extracellular space. Thus, reduced permeability is equivalent to the product of permeability surface area per unit volume of tissue. It would be preferable to use the commonly used unit of  $\text{minutes}^{-1}$  for expressing  $K^{\text{trans}}$ .<sup>2</sup>

Precise methodology for imaging BBB permeability is extremely important. Chronic neurodegenerative disease could result in minimal BBB leakage, whereas a brain tumor causes massive BBB leakage with very high  $K^{\text{trans}}$  values. A minimal change in chronic neurodegenerative disease, in terms of  $K^{\text{trans}}$  values, may present difficulties in discriminating the normal and targeted neurodegenerative condition.<sup>3</sup> Hence, neuroradiologists and clinical researchers should be aware of the potential problems when dealing with imaging results of BBB permeability.

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