Blood-Brain Barrier Leakage in Early Alzheimer Disease Response

preliminary results for differentiation of malignant and benign thoracic lesions. Radiology 2016;279(2):578–589.

2. Togao O, Kessingeer CW, Huang G, et al. Characterization of lung cancer by amide proton transfer (APT) imaging: an in-vivo study in an orthotopic mouse model. PLos One 2013;8(10):e77019.

3. Vinogradov E, Sherry AD, Lenkinski RE. CEST: from basic principles to applications, challenges and opportunities. J Magn Reson 2013;229:155–172.

4. van Zijl PC, Yadav NN. Chemical exchange saturation transfer (CEST): what is in a name and what isn't? Magn Reson Med 2011; 65(4):927–948.

5. Zhou J1, Wilson DA, Sun PZ, Klaus JA, Van Zijl PC. Quantitative description of proton exchange processes between water and endogenous and exogenous agents for WEX, CEST, and APT experiments. Magn Reson Med 2004;51(5):945–952.

Response

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We thank Dr Kim and colleagues for their interest in and valuable comments about our article (1). As they indicated, CEST including APT has various challenges: respiratory motion artifacts in human lung, low sensitivity of the APT signal, and effectiveness of B1 power. We agree that the addition of experiments regarding interimage agreement between two images of the same lesion would have further strengthened our study.

With regard to the normalized saturation effect of S_{sat}/S_0, the values more than 1 are no greater than 1.05 or 5%, which is considered within the normal error range. We have set S_{sat}/S_0 as 1 as measured at either end of a farthest frequency of +10 or −10 ppm from the center frequency; therefore, almost no saturation effect is observed. The variation of offset frequency values for the lung could be caused by respiratory motion artifacts (2). When compared with that in the stationary brain, the variation in the lung is expected to be greater due to respiratory and cardiac motion. We have used the subtraction between the values at +3.5 ppm and −3.5 ppm for MTR_{asym} and presented the absolute value; therefore, we were not concerned with the elevated signal in the z-spectrum.

Regarding the suggestion of a phantom experiment to further evaluate the saturation effect, we have performed an egg white phantom experiment to investigate the CEST effect as a preliminary experiment. We found that the MTR_{asym} value at 3.5 ppm by using a B1rms of 1.0–2.0 μT yields an increasing APT value (unpublished data, October, 2016). Respiratory motion artifact is most likely the cause for the CEST color map in the lesion showing a large area with a MTR_{asym} value of almost 10%. This drawback should have been stated as one of the limitations in our study.

Because of the limitation in the number of figures, we were not able to include MTR_{asym} spectra and a CEST sequence diagram. We certainly appreciate these valuable comments made and will consider them in our future investigations.

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References

1. Ohno Y, Yui M, Koyama H, Yoshikawa T, Matsumoto S, Seki S, Miyazaki M, Ouyang C, and Sugimura K. Chemical exchange saturation transfer (CEST) imaging: preliminary experience for differentiation of malignant from benign tumors. Radiology 2016;279(2): 578–589.

2. Togao O, Kessingeer CW, Huang G, et al. Characterization of lung cancer byamide proton transfer (APT) imaging: an in-vivo study in an orthotopic mouse model. PLos One 2013;8(10):e77019.

Blood-Brain Barrier Leakage in Early Alzheimer Disease

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Editor:

We read with much interest the article by Dr van de Haar and colleagues in the November 2016 issue of *Radiology* (1) regarding blood-brain barrier (BBB) leakage in patients with early Alzheimer disease.

Reportedly, dynamic contrast material–enhanced (DCE) magnetic resonance (MR) imaging is promising for the exploration of BBB leakage (2). However, some technical issues in the current study may limit its conclusions.

First, the use of a venous input artificially displaced the vascular peak, which is visualized after the tissue peak, as shown in figure 1. It may provide calculated-related artifacts, which might be corrected by adding a negative temporal delay parameter. An arterial input function remains more accurate than a venous input function for the calculation of DCE imaging parameters (3).

Second, the pharmacokinetic two-compartments model used to calculate BBB leakage employed the Patlak technique, which provides data only on the permeability (or leakage rate) and the blood plasma volume (4). This model assumes that the contrast agent concentration is equal in the large vessels and in the vascular compartment of the tissue. In case of minor leakage rates, the contrast agent concentration in the gray matter should be proportional with the contrast agent concentration in the venous blood, which is not in line with the curves shown in figure 1. The attenuation of the initial peak in the gray matter may be explained by a limited blood flow, which is not included in the model.

Third, the evaluation of the blood volume may be underestimated with the Patlak technique, leading to a possible overestimation of the leakage rate. To limit this effect, the "equilibration time" or t* has to be defined, and points before t* are commonly removed (5). Such a correction is not mentioned here.

Fourth, the assumption of Gaussian distribution used to estimate and correct the noise is interesting but might not be relevant because of the previously described potential overestimation of the leakage rate and the Rician noise in the tissue, especially at the end of the tissue curves.

In conclusion, one should remain cautious when interpreting these results, which must be confirmed with further studies.

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References

1. van de Haar HJ, Burgmans S, Jansen JFA, et al. Blood-brain barrier leakage in patients with early Alzheimer disease. Radiology 2016;281(2):527–535.
2. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 2008;57(2):178–201.
3. Cheng HLM. Investigation and optimization of parameter accuracy in dynamic contrast-enhanced MRI. J Magn Reson Imaging 2008;28(3):736–743.
4. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 1983;3(1):1–7.
5. Zhou Y, Ye W, Brašić JR, Crabb AH, Hilton J, Wong DF. A consistent and efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. NeuroImage 2009;44(3):661–670.

Response

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Dr Lecler and colleagues comment on theoretical aspects of the kinetic modeling used in our study on BBB leakage measurements (1). Models employed in imaging studies are frequently discussed and should always be carefully designed, validated, and tested for reproducibility (2). Therefore, we are happy to respond to these comments.

First, they noted the time delay of the venous input function to the first tissue peak and prefer an arterial input function. Ideally, the arterial input function would be used to model the transit of contrast agent from the artery, through capillaries into the vein. However, measurement of the arterial input function is less stable than venous measurements (3,4).

Second, it is suggested that more advanced models should be used incorporating flow. However, previous simulations convincingly showed that the Patlak approach provided the best low leakage measurements (5,6) independent of flow (7).

Third, the blood and tissue time courses in figure 1 become nearly proportional after the so-called equilibrium time. At earlier phases, the flow indeed affects both blood and tissue curves and we accounted for this effect by using robust linear regression. This algorithm determines the slope from the later data points as the earlier points were more variable (8). These later data points are independent of flow and delay in venous input function. In fact, by using fast sampling before the equilibrium time, the integral of the vascular input function (abscissa of Patlak plot) can be accurately calculated, avoiding overestimation of blood volume. Moreover, realistic blood plasma volumes were obtained approximating those in the literature (9).

Fourth, we see that the noise classification was not completely understood. The calculated histogram of leakage rates is highly symmetric, but has not necessarily a Gaussian shape. We disagree that the concentration curves should follow Rician noise as these are calculated from MR signals with a sufficiently high signal-to-noise ratio.

Currently, no consensus on the exact implementation of kinetic modeling of subtle BBB leakage has been reached and in vivo validation remains difficult. Some of the suggested corrections would influence the numerical values, but the group effects and conclusion of increased BBB leakage in Alzheimer disease will remain the same, which is confirmed by another research site (10).

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References

1. van de Haar HJ, Burgmans S, Jansen JFA, et al. Blood-brain barrier leakage in patients with early Alzheimer disease. Radiology 2016; 281(2):527–535.
2. Wong SM, Zhang CE, Jansen JFA, et al. Measuring subtle leakage of the blood-brain barrier in cerebrovascular disease: how reproducible is DCE-MRI? JMRI doi: 10.1002/jmri.25540.
3. Garpebring A, Wirestam R, Ostlund N, Karlsson M. Effects of inflow and radiofrequency spoiling on the arterial input function in dynamic contrast-enhanced MRI: a combined phantom and simulation study. Magn Reson Med 2011;65(6):1670–1679.
4. Roberts C, Little R, Watson Y, et al. The effect of blood inflow and B(1)-field inhomogeneity on measurement of the arterial input function in axial 3D spoiled gradient echo dynamic contrast-enhanced MRI. Magn Reson Med 2011;65(1):108–119.
5. Barnes SR, Ng TSC, Montagne A, et al. Optimal acquisition and modelling parameters for accurate assessment of low Ktrans blood-brain barrier permeability using dynamic contrast-enhanced MRI. Magn Reson Med 2016;75(5):1967–1977.
6. Cramer SP, Larson HBW. Accurate determination of blood-brain barrier permeability using dynamic contrast-enhanced T1-weighted MRI: a simulation and in vivo study on healthy subjects and multiple sclerosis patients. J Cereb Blood Flow Metab 2014;34(10):1655–1665.
7. Larsson HBW, Courivaud F, Rostrup E, et al. Measurement of brain perfusion, blood volume, and blood-brain barrier permeability, using dynamic contrast-enhanced T1-weighted MRI at 3 Tesla. Magn Reson Med 2009;62(5):1270–1281.
8. van de Haar HJ, Jansen JFA, van Osch MJ, et al. Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging. Neurobiol Aging 2016; 45:190–196.
9. Heye AK, Thrippleton MJ, Armitage PA, et al. Tracer kinetic modelling for DCE-MRI quantification of subtle blood-brain barrier permeability. NeuroImage 2016;125:446–455.
10. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron 2015;85(2): 296–302.

Histopathologic Assessment of Neurotoxicity after Repeated Administration of Gadodiamide in Healthy Rats

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Editor:

We read with great interest the article by Dr Smith and colleagues on accumulation and partial clearance of gadolinium from the brain after repeated administration of gadodiamide in a rodent model with intact blood-brain barrier, which was recently published online in *Radiology* (1). The authors state that there was no "detectable neurotoxicity" and no "histopathologic consequence" after up to 20 doses of intravenously administered gadodiamide with a cumulative dose of up to 12 mmol/kg. While it is certainly encouraging that the authors could not detect any extensive tissue damage, we are concerned that the histopathologic assessment limits such conclusions.

First, contrary to guidelines for toxicologic histopathology, pathologists were not made aware of the different treatment groups, as is recommended for evaluations where a known toxic syndrome with a defined spectrum of lesions does not exist (2,3).

Second, and more importantly, neurotoxicity assessments were not specified, making comparison with independent studies impossible. Stereological evaluation would allow quantification of neuronal cell number and volume (4). Furthermore, only standard hematoxylin-eosin (H-E) stains were mentioned, which have limited sensitivity in detecting subtle changes associated with potential gadolinium-related neurotoxicity such as impaired mitochondrial function (5). Assessment of pathologic changes on this level would require methods such as lactate dehydrogenase immunoreactivity or electron microscopy. In addition, it is known that glial cells react to neurotoxic events (6), and previous studies found gadolinium to be deposited mostly within or in close proximity to the endothelial wall (7). Therefore, a critical evaluation of potential gadodiamide-related neurotoxicity should include quantitative measures of reactive astrogliosis and microglial activation. While not strictly required for toxicologic assessments according to current guidelines (3), we believe that a statement like the one made by Dr Smith and colleagues would need to be based on appropriate evaluation and quantification of neuronal function.

In addition, gadolinium is regularly used in conditions with an impaired blood-brain barrier, leading to a different risk profile for gadolinium accumulation. For example, we and other investigators recently provided evidence of gadolinium deposition in patients with multiple sclerosis within routine clinical care (8). In conclusion, we do not believe that the shown representative normal -ppearing H-E images alone exclude gadolinium-related neurotoxicity, especially in conditions with potentially increased gadolinium uptake in the brain.

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