Letter to the Editor

A reduction of perfusion can lead to an artificial elevation of slow diffusion measure: examples in acute brain ischemia MRI intravoxel incoherent motion studies

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Intravoxel incoherent motion (IVIM) theory in magnetic resonance imaging (MRI) was proposed by Le Bihan *et al.* to account for the effect of vessel/capillary perfusion on the aggregate diffusion weighted MR signal. The fast component of diffusion is related to micro-perfusion, whereas the slow component is linked to water molecular diffusion. Three parameters can be computed. D_{slow} (or *D*) is the diffusion coefficient representing the slow "pure" water molecular diffusion (unaffected by perfusion). The perfusion fraction (PF, or *f*) represents the fraction of the compartment related to (micro)circulation, which can be understood as the proportional "incoherently flowing fluid" (i.e., blood) volume. D_{fast} (or *D**) is the perfusion-related diffusion coefficient representing the incoherent microcirculation within the voxel, which holds information for blood perfusion's speed. Among IVIM research community, it has been generally assumed that the perfusion component and the diffusion component can be separately determined. We recently reported that, for the liver, IVIM modeling of the perfusion component is constrained by the diffusion component, and a reduced D_{slow} measure leads to artificially higher PF and D_{fast} measures (1,2). Two related questions would then follow: Is this phenomenon also observed in organs other than the liver? Can a reduction of PF lead to an artificial elevation of D_{slow} measure? We argue that the answer is "yes" to both questions. Hereby, we explain this point by using examples in existing brain IVIM literatures with acute PF change being the initiating factor. These examples suggest a lower PF can lead to a higher observed D_{slow}.

By increasing arterial carbon dioxide pressure ($PaCO_2$), McKinstry *et al.* (3) induced brain grey matter perfusion increases in three dogs and IVIM imaging of the brain was acquired. $PaCO_2$ was changed according to the order of: low $PaCO_2$, high $PaCO_2$, and normal $PaCO_2$. Their IVIM analysis in Fig-5 shows, among various $PaCO_2$, PF and D_{slow} changed toward the opposition directions. When PF went up, D_{slow} went down; when PF went down, D_{slow} went up. Pavilla *et al.* (4) studied cerebral hypoperfusion induced by hyperventilation challenge in 10 healthy volunteers. For the IVIM measures, they reported cerebellum grey matter had PF of 0.16±0.07 under normal ventilation and 0.07±0.09 (P=0.03) under hyperventilation, while D_{slow} was 0.55±0.10 and 0.63±0.13 ($\times 10^{-3}$ mm^2/s, P=0.05) respectively under normal ventilation and hyperventilation. Thus, hyperventilation included lower PF and higher D_{slow} measures in cerebellum grey matter. In the study by Xu *et al.* (5), a middle cerebral artery occlusion model was established in 24 beagle dogs, and IVIM imaging data were acquired at 4.5 hours after model establishment. Serum soluble CD40L level was used as an indicator of microvascular thrombosis after acute ischemic stroke onset, with its higher level associated with more microvascular thrombosis events

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and thus lower perfusion in the ischemic stroke lesions (5,6). Their Fig-5A (for D_{slow}) and Fig-5B (for PF) show a potential negative correlation between PF and D_{slow}. Compared with the contralateral healthy brain hemisphere [PF =0.055±0.008, D_{slow} =(0.813±0.152)×10^{-3} mm^2/s], the stroke lesions had lower PF and low D_{slow}. However, the stroke lesions with higher serum soluble CD40L level and lower PF (0.041±0.007) had higher D_{slow} (0.531±0.153) than D_{slow} (0.435±0.044, P=0.057) of the stroke lesions with lower serum soluble CD40L level and higher PF (0.051±0.007, P<0.001). With IVIM measures of 20 acute ischemic stroke patients, Zhu *et al.* (7) reported penumbra zone, ipsilateral non-ischemia region, and contralateral healthy hemisphere had PF of 0.0541±0.0323, 0.0755±0.0454, and 0.0722±0.0293 respectively, while the corresponding D_{slow} measure was 0.847±0.116, 0.819±0.225, 0.842±0.100 (×10^{-3} mm^2/s) respectively, with the lowest PF associated with highest D_{slow} and highest PF associated with lowest D_{slow}.

In interpreting the relationship between PF and D_{slow}, it should be noted that acute brain ischemia (with a reduction of PF) can indeed induce cytotoxic edema resulting in a reduction of D_{slow} (8,9). When both PF and D_{slow} are truly decreased and the decrease of D_{slow} is of sufficient extent, D_{slow} can be measured as "decreased" [such as the case for IVIM measure of brain ischemic core (7-9)]; though a possibility remains that, even for such decreased D_{slow} measures, their observed value is still over-estimated. On the other hand, there likely is a PF change magnitude window which does not induce observed D_{slow} reduction but instead induce observed D_{slow} artificial elevation. As time goes on, ischemia induced cytotoxic edema may turn into vasogenic edema which will demonstrate a true D_{slow} elevation (8,9). In the examples of McKinstry *et al.* (3), Pavilla *et al.* (4) and Xu *et al.* (5), brain changes or lesions would not have had dominant vasogenic edema with overall true D_{slow} elevation. In the example of Zhu *et al.* (7), for the retrospective cohort of stroke patients with vessel occlusion, the mean time from onset to treatment was 8.3±5.1 hours and MRI was conducted before the treatment, it is still more likely that there was no sufficient vasogenic edema leading to overall true D_{slow} elevation.

The point discussed here will have important implications in interpreting IVIM data. For example, in the report by Zhu *et al.* (7), the penumbra zone had a decreased PF of 0.0541±0.0323 (normal: 0.0722±0.0293, ischemic core: 0.0445±0.0262), while the observed D_{slow} was (0.847±0.116)×10^{-3} mm^2/s [normal: (0.842±0.100)×10^{-3} mm^2/s, ischemic core: (0.544±0.111)×10^{-3} mm^2/s]. Considering the degree of PF reduction, there could be a possibility that penumbra zone's true D_{slow} had decreased, the observed D_{slow} which was normal (or slightly higher than normal) was masked by an artificial increase of D_{slow} measure due to true reduction of PF. Moreover, the results of McKinstry *et al.* (3) and Zhu *et al.* (7) also suggest the possibility that a truly increased PF can lead to an artificial lowering of D_{slow} measure. In the study of McKinstry *et al.* (3), when a PF increase was induced by increasing $PaCO_2$, a lowering of D_{slow} was noted. In the results of Zhu *et al.* (7), compared with the contralateral healthy brain, the ipsilateral non-ischemia region had slightly higher PF measure (0.0755±0.0454) than that of the contralateral brain (PF: 0.0722±0.0293) which would have been caused by collateral blood flow compensation (10), resulting in a slightly lower D_{slow} measure than that of the contralateral brain (0.819±0.225 *vs.* 0.842±0.100 ×10^{-3} mm^2/s).

Taking together the evidence explained here and our previously discussions (1,2), it can be summarized that, if one component, being perfusion component or diffusion component, changes toward one direction (i.e., increase or decrease), the other component will be constrained to change toward the opposite direction to a certain extent. For this problem, one might expect the cause could be that currently prevalent IVIM modeling does not fully consider the varied noise proportions of diffusion weighted images scanned under different acquisition conditions (11). However, our preliminary further analysis showed noise correction only slightly improved this "constraining". Moreover, the prevalent IVIM modeling is based on Eq. [1]:

$$SI_{(b)}/SI_{(0)} = (1-PF)\times\exp(-b\times D_{slow}) + PF\times\exp(-b\times D_{fast}) \quad [1]$$

where $SI_{(b)}$ and $SI_{(0)}$ denote the signal intensity of images acquired with the *b*-factor value of *b* and *b* =0 s/mm^2, respectively. With higher *b*-value associated lower image signal of the target tissue, Eq. [1] is focused on describing the signal decay pattern along increasingly higher *b*-values by three IVIM parameters (PF, D_{slow}, D_{fast}). Signal intensity at each *b*-value [i.e., $SI_{(b)}$] is normalised by the signal intensity of *b* =0 image [i.e., $SI_{(0)}$]. Applying this approach, for example if we want to compare the IVIM parameters of the normal brain and a brain tumor, we will take $SI_{(0)}$ of the normal brain and $SI_{(0)}$ of the tumor both as 1 (or 100) for the biexponential decay modelling, thus we would be assuming the $SI_{(0)}$ of the normal brain and the $SI_{(0)}$ the

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tumor are equal. This could be invalid in many scenarios. We demonstrated that an initial lower $SI_{(0)}$ of the target tissue is associated with a lower D_{slow} and a higher PF (1,2,11,12), regardless of whether we used segmented fitting or full fitting (1). Regardless of whatever methods we use to fit the curve of the diffusion weighted imaging signal decay along increasingly higher *b*-values, IVIM parameters are determined by this curve's pattern which is in turn determined by relativity of $SI_{(b)}$ to $SI_{(0)}$. Therefore, target tissues of different compositions, which have different $SI_{(0)}$, may not necessarily be directly compared with the three IVIM parameters. For example, if two living tissues had the same diffusion and perfusion as well as other biological properties but these two tissues had different iron contents, we would expect the tissue with higher iron content would have lower $SI_{(0)}$, lower measured D_{slow}, and higher measured PF (12). We consider this problem is not easily solvable by a better fitting approach, by high signal-to-noise images, or by an extensive array of *b*-value images. Further research to better separate diffusion component and perfusion component should be pursued (1,13). Another possible approach would be that, if the reference values of IVIM diffusion and perfusion components are already known with standardised data acquisition, then we may be able to understand how these constrains can be computationally compensated for each target tissue.

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