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

Running title: Perfusion reduction leads to artificial Dslow elevation.

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Abstract

Intravoxel incoherent motion (IVIM) theory in 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 molecular diffusion. Among IVIM research community, it has been generally assumed that the perfusion component and the diffusion component can be separately determined. However, we recently published 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. 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? I argue that the answer is 'yes' to both questions. Hereby I explain this point by using examples in existing brain IVIM literatures with acute PF change being the initiating factor. These examples demonstrate a lower PF can lead to a higher observed $D_{slow}$. 
Intravoxel incoherent motion (IVIM) theory in 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 molecular diffusion. Three parameters can be computed. $D_{\text{slow}}$ (or $D$) is the diffusion coefficient representing the slow ‘pure’ 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. $D_{\text{fast}}$ (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. However, in *NMR in Biomedicine* we recently published that, for the liver, IVIM modeling of the perfusion component is constrained by the diffusion component, and a reduced $D_{\text{slow}}$ measure leads to artificially higher PF and $D_{\text{fast}}$ 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 $D_{\text{slow}}$ measure? I argue that the answer is ‘yes’ to both questions. Hereby I explain this point by using examples in existing brain IVIM literatures with acute PF change being the initiating factor. These examples demonstrate a lower PF can lead to a higher observed $D_{\text{slow}}$.

By increasing arterial carbon dioxide pressure (Paco2), McKinstry et al. [3] induced brain grey matter perfusion increases in three dogs. Paco2 was changed according to the order of: low Paco2, high Paco2, and normal Paco2. Their Fig-5 unequivocally shows, among various Paco2, PF and $D_{\text{slow}}$ changed toward the opposition directions. When PF went up, $D_{\text{slow}}$ went down; when PF went down, $D_{\text{slow}}$ 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 $D_{\text{slow}}$ was 0.55±0.10 and 0.63±0.13 (p=0.05) respectively under normal ventilation and hyperventilation. Thus, hyperventilation included lower PF and higher $D_{\text{slow}}$ in cerebellum grey matter. In the study of Xu et al. [5], a middle cerebral artery occlusion model was established in 24 beagle dogs, and IVIM image 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 and thus lower perfusion in the ischemic stroke lesions [5, 6]. Their Fig-5A (for $D_{\text{slow}}$) and Fig-5B (for PF) show a potential negative correlation between PF and $D_{\text{slow}}$. Compared with the contralateral healthy brain hemisphere (PF= 0.055±0.008, $D_{\text{slow}}$= 0.813±0.152), the stroke lesions had lower PF and low $D_{\text{slow}}$. However, the stroke lesions with higher serum soluble CD40L level and lower PF (0.041±0.007) had higher $D_{\text{slow}}$ (0.531±0.153) than that of the stroke lesions ($D_{\text{slow}}$: 0.435±0.044, p=0.057) 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 [5] 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 $D_{\text{slow}}$ measure was 0.847±0.116, 0.819±0.225, 0.842±0.100 respectively, with the lowest PF associated with highest $D_{\text{slow}}$ and highest PF associated with lowest $D_{\text{slow}}$. Though the differences for IVIM values of ipsilateral non-ischemia region and contralateral healthy hemisphere may not be statistically significant in their study, the values for penumbra zone were paradoxical.

In interpreting the relationship between PF and $D_{\text{slow}}$, it should be noted acute brain ischemia (with a reduction of PF) can indeed induce cytotoxic edema resulting in a reduction of $D_{\text{slow}}$ [8]. When both PF and $D_{\text{slow}}$ are truly decreased and the decrease of $D_{\text{slow}}$ is of sufficient extent, $D_{\text{slow}}$ can still be measured as ‘decreased’ (such as the case for IVIM measure of brain ischemic core [7, 8]); though a possibility remains that, even for such decreased $D_{\text{slow}}$ 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 $D_{\text{slow}}$ reduction but instead induce observed $D_{\text{slow}}$ artificial elevation. As time goes on, ischemia induced cytotoxic edema may turn into vasogenic edema which will demonstrate a true $D_{\text{slow}}$ elevation [8]. In the examples discussed above, no lesion would have had dominant vasogenic edema with true $D_{\text{slow}}$ elevation.

The point discussed here will have important implications in interpreting IVIM data. For example, in the report of 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 $D_{\text{slow}}$ was 0.847±0.116 (normal: 0.842±0.100, ischemic core: 0.544±0.111). Considering the degree of PF reduction, there is high possibility that penumbra zone’s true $D_{\text{slow}}$ had decreased, the observed $D_{\text{slow}}$ which was normal (or slightly higher than normal) was masked by an artificial increase of $D_{\text{slow}}$ measure due to true reduction of PF. Moreover, the results 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 $D_{\text{slow}}$ measure. In the study of McKinstry et al [3], when a PF increase was induced by increasing Paco2, a lowering of $D_{\text{slow}}$ was noted. In the results of Zhu et al [6], 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 [9], and slightly lower $D_{\text{slow}}$ measure than that of the contralateral brain (0.819±0.225 vs. 0.842±0.100).

Taking together the evidence explained here and our previously discussions [1, 2], it may 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. Further research into IVIM modeling to better separate diffusion component and perfusion component should be pursued. 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 targeted tissue.

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