**Article:**
Moulin, K., Stoeck, C.T. orcid.org/0000-0001-8670-0929, Axel, L. et al. (15 more authors) (Cover date: December 2023) In Vivo Cardiac Diffusion Imaging Without Motion-Compensation Leads to Unreasonably High Diffusivity. Journal of Magnetic Resonance Imaging, 58 (6). pp. 1990-1991. ISSN 1053-1807

https://doi.org/10.1002/jmri.28703

**In Vivo Cardiac Diffusion imaging without motion-compensation leads to unreasonably high diffusivity**

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Acknowledgment: British Heart Foundation Grant RG/19/1/34160 for PFF and ADS.

**KEYWORDS:** Cardiac Diffusion Imaging, Cardiac IVIM, cDTI

**LIST OF ABBREVIATIONS:**
Diffusion-weighted imaging - DWI
Apparent diffusion coefficient – ADC
Mean diffusivity – MD
Diffusion ensor imaging - (DTI)
Intra-voxel incoherent motion (IVIM)



In tissue, water molecules move due to large physiological bulk motion, perfusion, or diffusion effects. Diffusion-weighted imaging (DWI) is a technique that aims to use motion-encoding gradient waveforms to sensitize the MR signal to the diffusion of water molecules. The diffusivity of water molecules is temperature driven and restricted and/or hindered by the tissue microstructure. At a normal body temperature of 37°C in a non-restricted environment, the diffusion coefficient of water is about $2.9x10^{-3}mm^2/s$, which is thus the physical upper limit of the observable diffusion coefficients in tissue[1]. Across diffusion models, several parameters may represent the diffusivity of water molecules in the extra- and intra-cellular tissue compartments, including the apparent diffusion coefficient (*ADC*), the mean diffusivity (*MD*) for the diffusion tensor imaging (DTI) model, or *D* (also called $D_{slow}$) for the Intra-voxel incoherent motion (IVIM) model; all are subject to the theoretical limit of $2.9x10^{-3}mm^2/s$.

The principal challenge of performing DWI accurately in the heart is to separate the motion of water molecules due to diffusion from that resulting from cardiac deformation. Traditional diffusion-encoding waveforms used in stationary tissues, such as the brain, are sensitive to cardiac motion and may lead to unwanted DWI signal attenuation and hence calculated diffusivities artifactually high (even $>2.9x10^{-3}mm^2/s$). Recently, advanced diffusion encoding strategies have been proposed, such as the STEAM approach[2] or motion-compensated diffusion encoding gradient waveforms [3], which reduce the impact of cardiac deformation. These motion compensation strategies have largely contributed to the development of cardiac DWI. As of today, more than 50 cardiac DWI studies using ADC, IVIM, or DTI models on healthy and pathologic cases have been published. As shown in Figure 1, none of the studies employing motion-compensation strategies have ever reported a diffusivity parameter above the theoretical limit.

However, the implementation of IVIM in the heart remains particularly challenging. Spinner et al.[4] have demonstrated that motion-compensated waveforms may alter the perfusion sensitivity of cardiac DWI used in the IVIM model. For this reason, STEAM sequences or retrospective motion compensation strategies may be preferred for IVIM. Nonetheless, it is evident that cardiac IVIM acquired without motion compensation strategies will result in corrupted images and erroneous results.

We, therefore, note with some concern that several recent cardiac DWI studies using the IVIM model have reported diffusivities clearly above $2.9x10^{-3}mm^2/s$: three research articles published in *JMRI*: Laissy et al. 2013[5] ($ADC$=6-$9.2x10^{-3}mm^2/s$), Mou et al. 2017[6] ($D_{slow}$=3.04-$3.37x10^{-3}mm^2/s$), Xiang et al. 2022[7] ($D$=4.30-$4.75x10^{-3}mm^2/s$); one observational study published in *Medicine*: Xiang et al. 2018[8] ($D$=1.7-$3.5x10^{-3}mm^2/s$); one case report published in *Frontiers in Cardiovascular Medicine*: Li et al. 2022[9] ($D_{slow}$=2.25-$3.5x10^{-3}mm^2/s$); and one ISMRM conference proceeding by Lan et al. 2018[10] ($D_{slow}$=3.77-$3.84x10^{-3}mm^2/s$). Some of these studies have been already the subject of a previous letter attributing these high diffusivities to cardiac motion[1]. It is worth noting that none of these studies used motion-compensation strategies. In addition, the cardiac DWI images shown in these studies all display remarkable signal loss in the myocardium, or even an absent myocardium[5–10]. To the best of our knowledge, these high diffusivity values can only be attributed to motion-corrupted DWI signals and shouldn't be considered a reliable report of cardiac diffusivity and thus not an accurate reflection of underlying tissue microstructure.


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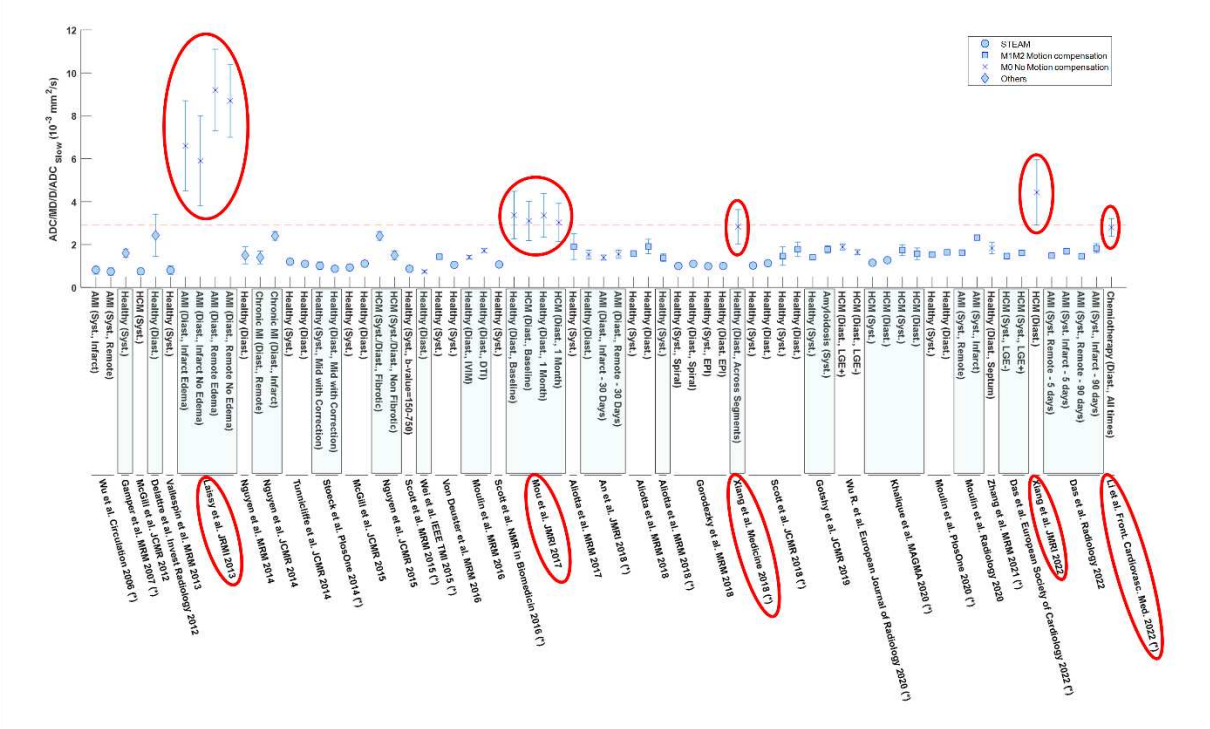


Figure 1: Cardiac diffusivities, ADC, MD, D or $D_{slow}$, reported from cardiac DWI studies from 2006 to 2022. Only studies reporting cardiac diffusivities in humans were included in this figure. Error bars represent the mean and standard deviation for different populations acquired in systole (Syst.) or diastole (Diast.) with the STEAM approach, second-order motion compensation (M1M2), non-motion-compensated (M0) or other encoding approaches (first-order motion compensation, diffusion preparation bSFFP encoding).The diffusivities of studies annotated by (*) were reformatted or recalculated to match the format of this figure. The red dashed line represents the theoretical limit of $2.9 \times 10^{-3} mm^2/s$. Studies circled in red were identified as above the theoretical limit.