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## Short-term repeatability of in vivo cardiac intravoxel incoherent motion (IVIM) tensor imaging in healthy human volunteers

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### Abstract

**Background:** Intravoxel incoherent motion (IVIM) tensor imaging is a promising technique for diagnosis, prognosis and treatment monitoring of cardiovascular diseases. Knowledge about measurement repeatability however remains limited.

**Purpose:** To evaluate short-term repeatability of IVIM tensor imaging in normal in vivo human hearts.

**Study Type:** Prospective.

**Population:** 10 healthy subjects without history of heart diseases.

**Field Strength/Sequence:** Balanced steady-state free-precession cine sequence and single-shot spin-echo echo planar IVIM tensor imaging sequence ( $b$ -values = 0, 10, 25, 50, 75, 100, 200, 300, 400 s/mm<sup>2</sup> and 6 diffusion-encoding directions) at 3.0 T.

**Assessment:** Subjects were scanned twice with an interval of 15 minutes, leaving the scanner between studies. Fractional anisotropy (FA), mean diffusivity (MD), mean fraction (MF), and helix angle (HA) were independently measured by two radiologists in the left ventricle (LV) wall of each subject.

**Statistical Tests:** IVIM tensor indexes were compared between different observers or scans using a paired t-test (normal data) or a Wilcoxon rank-sum test (non-normal data). Inter-observer agreement and short-term test-retest repeatability were assessed using the intra-class correlation coefficient (ICC), within coefficient of variation (CV) and Bland-Altman limits of agreements (BA-LA).

**Results:** Interobserver repeatability was excellent for all IVIM tensor indexes (ICC: 0.807~0.930; WCV: 1.13%~8.22%). Short-term test-retest repeatability was excellent for MD of the self-diffusion tensor ( $\mathbf{D}$ ) and MF of the perfusion fraction tensor ( $\mathbf{f}_p$ ) (ICC: 0.806~0.875; WCV: 1.44%~9.99%) and moderate for FA and MD of the pseudo-diffusion tensor ( $\mathbf{D}^*$ ) (ICC: 0.454~0.560; WCV: 7.04%~13.12%). Other indexes presented good test-retest repeatability (ICC: 0.785~0.752; WCV: 3.16%~7.61%).

**Data Conclusion:** The indexes of  $\mathbf{D}$  and  $\mathbf{f}_p$  tensors exhibited satisfactory measurement repeatability in in vivo cardiac IVIM tensor imaging, but further efforts should be made to improve the measurement repeatability of  $\mathbf{D}^*$  tensor indexes.

**Key words** Intravoxel incoherent motion; Diffusion tensor imaging; In vivo human heart; Short-term repeatability

## Introduction

Intravoxel incoherent motion (IVIM) theory, which was initially proposed by Le Bihan et al., indicates that MR signal loss in diffusion-weighted (DW) imaging (DWI) is caused by two phenomena: isotropic self-diffusion due to Brownian motion of water protons in extravascular space and isotropic pseudo-diffusion (or perfusion) due to bulk motion of water protons in randomly oriented capillaries<sup>1,2</sup>. Thus, a bi-exponential IVIM model has been established to quantify both phenomena<sup>2</sup>. The introduction of this model provides a unique method for simultaneous measurement of tissue diffusion and perfusion parameters without the need to resort to contrast agent<sup>3</sup>. In recent years, IVIM imaging based on the bi-exponential model has undergone rapid development with successful applications in a variety of body parts, such as neural system<sup>4,5</sup>, liver<sup>6,7</sup>, kidney<sup>8,9</sup> and pancreas<sup>10,11</sup>. In addition to brain and abdominal organs, IVIM imaging has also been attempted in the ex vivo and in vivo heart<sup>12,13</sup>.

However, the majority of fibers and capillaries in myocardium are ordered or exhibit anisotropy in morphology<sup>14,15</sup>. Hence, the assumption that the motion of cellular water and the flow of vascular water are isotropic, as in the original IVIM theory, is no longer true for myocardial tissues. This means that the IVIM parameters derived from the bi-exponential model cannot accurately reflect the features of myocardial structure and function. Indeed, a directional dependence of self-diffusion and pseudo-diffusion parameters on diffusion-encoding direction has been observed in cardiac IVIM imaging<sup>16</sup>. To cope with this problem, Abdullah et al. put forward an intravoxel incoherent motion-diffusion tensor imaging (IVIM-DTI) model where both scalar self-diffusion ( $D$ ) and pseudo-diffusion ( $D^*$ ) parameters in the bi-exponential IVIM model were formulated as rank-2 tensors<sup>17</sup>. The ability of the IVIM-DTI model to describe the orientational preference of myocardial fibers and capillaries has been validated in perfused isolated heart experiments<sup>17</sup>. An improved tensor formalism for all IVIM parameters has since been proposed and is referred to as the IVIM tensor model<sup>18</sup>. This IVIM tensor model has recently been used in an attempt to characterize the in vivo human heart<sup>19</sup>.

In contrast to the conventional DTI model and the scalar IVIM model, the IVIM tensor model accounts not only for diffusion anisotropy, but also for potential anisotropy of the blood flow compartment. In view of this unique ability, the IVIM tensor imaging technique could be expected to offer a fresh perspective to predict, classify and diagnose cardiovascular diseases with morphologic abnormalities of microstructure and microcirculation. Nevertheless, it should be emphasized that IVIM tensor analysis relies on the acquisition of multi-directional and multi- $b$ -value DW images<sup>18,19</sup> and that the DW images are susceptible to cardiac and respiratory motions<sup>20</sup>. Hence, when IVIM tensor imaging is applied in sequential assessments of cardiovascular diseases and treatment response, the changes in measurements may reflect not only actual changes of myocardial microstructure and microcirculation but also errors resulting from heartbeat and breathing motion. Therefore, it is critical to evaluate the repeatability of in vivo cardiac IVIM tensor imaging before it is applied in clinical practice. Although some previous studies have reported the repeatability of DTI and scalar IVIM imaging in the in vivo heart<sup>21,22</sup>, there is limited knowledge on the repeatability of IVIM tensor imaging.

Thus the aim of the present study was to prospectively evaluate reliability and robustness of in vivo cardiac IVIM tensor imaging through assessing inter-observer agreement and short-term test-retest repeatability of IVIM tensor indexes in in vivo human hearts.

## Materials and Methods

### *Subjects*

This study was approved by our institutional Research Ethics Committee. Signed informed consent was obtained from each subject. Twelve subjects without history of heart diseases were recruited. The inclusion criteria were: a) healthy and b) at least 18 years old. Subjects with MRI contraindications (n=1) or who were unable to fully complete two scans (n=1) were excluded. Finally, ten healthy subjects were enrolled in this study, including 7 men and 3 women with a mean (standard deviation, SD) age of 28 (8) years (range: 21~47 years) and a mean (SD) heart rate of 54 (5) beats/min (range: 47~66 beats/min). All subjects were asked to fast for 4 hours before scanning.

### ***MRI Protocol***

Cardiac MRI was conducted on a 3.0 T digital scanner (Ingenia, Philips Healthcare, Eindhoven, Netherlands) using a digital stream anterior coil and a digital stream posterior coil. To assess the short-term repeatability of IVIM tensor indexes, the ten subjects were each scanned twice (subsequently referred to as test and retest). At the end of the first examination, the patients were asked to rest outside the MR scanning room. After about 15 minutes, the patients were repositioned on the MR table to perform the second examination. Both scans adopted the same imaging protocols and the positioning plan for the second scan was carefully matched to the first scan using anatomical landmarks.

After a series of localization steps to determine a mid-ventricular short-axis plane of the left ventricle (LV), a balanced steady-state free-precession cine sequence was executed to identify the end-diastolic pause. Then, IVIM tensor data were acquired during free-breathing on the slice of interest at the identified end-diastolic time point using a single-shot spin-echo echo planar imaging sequence with monopolar diffusion-encoding gradients and spectral pre-saturation with inversion recovery fat suppression management. Slice tracking navigation with a tracking factor of 0.6 was controlled by a pencil-beam navigator placed on the dome of the right hemidiaphragm. A 6 mm gating window was positioned around the end-expiratory position to discard the DW images acquired during inspiration. The IVIM tensor imaging parameters were as follows: TR/TE 2 heartbeats/68 ms; flip angle 90°; in-plane resolution  $3.13 \times 3.41 \text{ mm}^2$ ; field of view  $260 \times 200 \text{ mm}^2$ ; reconstruction matrix size  $224 \times 224$ ; slice thickness 10 mm;  $b$ -values 0, 10, 25, 50, 75, 100, 200, 300, and 400  $\text{s/mm}^2$ ; and 6 vendor optimized diffusion-encoding directions. The IVIM tensor sequence was implemented 5 times in the same mid-ventricular slice for test and retest. The scan efficiency was an average of 67.5% for the IVIM tensor acquisition with the slice tracking navigation-gated technique. The total scan time of test or retest was approximately 19 min at a heart rate of 60 beats/min.

### ***Image Analysis***

The image analysis was implemented using MatLab (v. R2014a, MathWorks, Natick, MA). The DW images corrupted by artifacts due to cardiac and respiratory motions were identified and rejected on the basis of visual analysis. The DW images of different  $b$ -values, diffusion-encoding directions and acquisitions were registered using a 2D rigid subpixel image registration algorithm<sup>23</sup>. A region of interest (ROI) was defined to cover the mid-wall of LV myocardium, excluding the epi- and endocardial borders as well as papillary muscles for minimizing the impact of partial volume effects. For quantification purposes, the LV wall was divided into four equal angle segments (anterior, lateral, inferior, and septum). The signal-to-noise ratio (SNR) in each of four equal angle segments was calculated from the trace DW images using the method described in Reeder et al. where SNR was defined as the ratio of mean signal to SD across multiple acquisitions in each voxel<sup>24</sup>. The mean SNR obtained in each segment was further averaged over six diffusion-encoding gradient directions for each subject.

The bi-exponential IVIM model is expressed as:

$$\frac{S(b)}{S_0} = f_d e^{-bD} + f_p e^{-bD^*} \quad (1)$$

where  $S_0$  is  $S(b)$  at  $b=0$  s/mm<sup>2</sup>,  $S(b)$  the signal intensity at a given  $b$ -value,  $D$  the self-diffusion coefficient,  $f_d$  the self-diffusion fraction,  $D^*$  the pseudo-diffusion coefficient, and  $f_p$  the pseudo-diffusion (or perfusion) fraction.

The IVIM tensor model for above all scalar IVIM parameters is formulated as:

$$\frac{S(b)}{S_0} = g^T \mathbf{f}_d g e^{-bg^T \mathbf{D} g} + g^T \mathbf{f}_p g e^{-bg^T \mathbf{D}^* g^T} \quad (2)$$

where  $g$  represents the normalized diffusion-encoding gradient vector,  $b$  designates the scalar nominal  $b$ -value, and  $\mathbf{D}$ ,  $\mathbf{f}_p$  ( $g^T \mathbf{f}_d g = 1 - g^T \mathbf{f}_p g$ ) and  $\mathbf{D}^*$  are rank-2 tensors, which represent the self-diffusivity, pseudo-diffusion (or perfusion) fraction and pseudo-diffusivity, respectively.  $\mathbf{D}$ ,  $\mathbf{f}_p$  and  $\mathbf{D}^*$  tensors are collectively called *IVIM tensors* in the following sections.

The scalar IVIM parameter in Eq. (1) is essentially the projection of the corresponding tensor in Eq. (2) along the diffusion-encoding gradient direction.

The IVIM tensor indexes were estimated on the averaged DW images from the five acquisitions. First, for each diffusion-encoding gradient direction, the projections of the IVIM tensors were derived using a Bayesian shrinkage prior (BSP) inference method that was proved to be more robust than least-squares fitting in IVIM parameter estimation<sup>25</sup>. Second,  $\mathbf{D}$ ,  $\mathbf{f}_p$  and  $\mathbf{D}^*$  tensors were generated on their respective 6 projections using the tensor estimation approach of Barmoutis et al<sup>26</sup>. After that, the eigensystem (eigenvalues and eigenvectors) was calculated for each tensor. Finally, fractional anisotropy (FA) and mean diffusivity (MD) of all IVIM tensors as well as helix angle (HA) of  $\mathbf{D}$  tensor were computed on the basis of the obtained eigensystem. For the  $\mathbf{f}_p$  tensor, MD was replaced with MF (mean fraction) in this study. In addition, HA analysis of  $\mathbf{D}$  tensor was performed on myocardium segmented transmurally into endocardial, mesocardial and epicardial layers. This segmentation was achieved by dividing the local myocardium into three equal thickness layers.

The above analyses (including evaluation of in vivo cardiac DW image quality, delineation of ROI in the LV wall, measurement of SNR in each of four equal angle segments, and calculation of IVIM tensor indexes) were independently performed by two radiologists (observer I, \*\* with 15 years experience in MRI reading and observer II, \*\* with 7 years experience in MRI reading) on the test and retest data. The measurements were averaged on both observers (or both scans) and then used to conduct the following parameter comparison and repeatability analysis between different scans (or different observers).

### **Statistical Analysis**

The statistical analyses were conducted using SPSS 25.0, (IBM, Chicago, IL) and Medcalc 11.4.2.0 (Mariakerke, Belgium). The median values of SNRs and IVIM tensor indexes in each segment or each layer (only for HA) were recorded and compared between different observers or scans using a paired t-test (for normally distributed data) or a Wilcoxon rank-sum test (for non-normally distributed data). Additionally, the differences of these parameters between segments or layers were assessed by one-way analysis of variance (ANOVA).  $P < 0.05$  was considered statistically significant.

Inter-observer repeatability of IVIM tensor indexes was assessed by calculating the intra-class correlation coefficient (ICC) and the within coefficient of variation (WCV). Test-retest repeatability was evaluated by calculating WCV, ICC, and 95% Bland–Altman limits of agreements (BA-LA). According to the recommendations of the Quantitative Imaging Biomarkers Alliance (QIBA)<sup>27</sup>, we defined the repeatability of IVIM tensor indexes as excellent when WCV was  $\leq 10\%$  and ICC was between 0.81~1, good when WCV was between 10~20% and ICC was between 0.61~0.8, moderate when WCV was between 20~30%

and ICC was between 0.41~0.6, and poor when WCV was >30% and ICC was  $\leq 0.4$ . If the WCV and ICC of any index corresponded to different WCV and ICC repeatability levels, the lower one was adopted.

## Results

The mean numbers of rejected cardiac DW images were  $6.5\% \pm 2.7\%$  and  $6.3\% \pm 2.9$  over 10 subjects for observers I and II, respectively. There was no significant difference in the rejected numbers between two observers.

### *SNR Estimation*

The averaged SNRs for two observers on test and retest as a function of  $b$ -value for four equal angle segments are plotted in Figure 1 and show that SNR decreased with increasing  $b$ -values. SNRs in the inferior segment were significantly lower compared with the other three segments for both test and retest. Thus, the IVIM tensor indexes obtained from the inferior segment were excluded from subsequent statistical analysis. In addition, there were no significant differences between test and retest for SNR of each segment.

### *Interobserver Repeatability*

Interobserver repeatability was excellent for all IVIM tensor indexes (ICC: 0.807~0.930; WCV: 1.13%~8.22%), as summarized in Tables 1 and 2. Also, no significant differences were observed between IVIM tensor indexes for different observers ( $P=0.095\sim 0.987$ ) or between segments ( $P=0.425\sim 0.884$ ). However, the HA of  $\mathbf{D}$  tensor significantly decreased from the epicardium ( $32.59\pm 4.37^\circ$  and  $32.85\pm 3.65^\circ$  for observers 1 and 2 respectively) to the endocardium ( $-27.01\pm 4.99^\circ$  and  $-27.70\pm 5.56^\circ$  for observers 1 and 2 respectively) passing through the mesocardium ( $3.57\pm 0.78^\circ$  and  $3.40\pm 0.98^\circ$  for observers 1 and 2 respectively) (Table 2).

### *Test-Retest Repeatability*

The means and SDs of IVIM tensor indexes over all subjects as well as ICC and WCV for test and retest are provided in Tables 3 and 4. There were no statistically significant differences in these indexes between the repeated scans ( $P>0.05$  in all cases) and between the equal angle segments ( $P=0.282\sim 0.952$ ). The significant variations of HA of  $\mathbf{D}$  tensor throughout the three myocardial layers was still observed (Table 4). Test–retest repeatability of the IVIM tensor indexes was excellent for MD of  $\mathbf{D}$  tensor and MF of  $\mathbf{f}_p$  tensor (ICC: 0.806~0.875; WCV: 1.44%~9.99%), but was moderate for FA and MD of  $\mathbf{D}^*$  tensor (ICC: 0.454~0.560; WCV: 7.04%~13.12%). Other indexes presented good repeatability (ICC: 0.785~0.752; WCV: 3.16%~7.61%). The test-retest Bland–Altman plots for lateral, anterior and septal segments are illustrated in Figures 2, 3 and 4 respectively and for HA in Figure 5. The maps of IVIM tensor indexes from a typical subject on the two scans are shown in Figure 6, and the corresponding 3D tensor fields are visualized in Supplemental Figure 1.

## Discussion

This work evaluated the reliability and robustness of IVIM tensor indexes in in vivo human hearts. The lateral, anterior and septal segments of the LV wall presented significantly higher SNR than the inferior segment in the DW images obtained from multiple acquisitions. In the three segments with superior SNR, test-retest repeatability was excellent or good for the  $\mathbf{D}$  and  $\mathbf{f}_p$  tensor indexes, but was just moderate for the  $\mathbf{D}^*$  tensor indexes. Inter-observer repeatability was excellent for all IVIM tensor indexes.

Both DTI and scalar IVIM imaging have their respective merits, but each neglects the benefits of the other model. By combining these two imaging modalities, IVIM tensor imaging has the potential to not only noninvasively probe myocardial fiber architecture, but

also to give unique information on anisotropic organization and perfusion of capillaries in myocardium. However, multi-directional and multi- $b$ -value acquisitions may also lead to more variability of parameter estimates compared with only multi-directional (for DTI) or multi- $b$ -value (for scalar IVIM imaging) acquisitions in light of heartbeat and breathing in in vivo cardiac diffusion MRI (dMRI). The trigger delay in the present study was set at end-diastole corresponding to minimal motion (in-plane and through-plane) of the LV wall to reduce cardiac motion and a slice tracking navigator-gated mode was adopted to reduce respiratory motion and to improve the registration between different  $b$ -value and directional DW images acquired during free-breathing. The signal averaging approach based on multiple acquisitions was employed to further enhance the quality of DW images. These strategies enabled us to obtain comparable SNRs to those reported in the literature<sup>19,20</sup>. However, the SNR of the inferior segment was relatively poor. This is mainly due to the influence of gastric peristalsis. In addition, the inferior segment is further away from the receiving coil than the other three segments and prone to off-resonance dephasing due to the vicinity of the posterior vein.

For in vivo cardiac dMRI, the measured parameter values and their repeatability are influenced by the adopted data acquisition strategies, such as imaging sequence, breathing mode and motion-compensation approach. According to Scott et al., a stimulated echo acquisition mode (STEAM) cardiac DTI sequence can produce lower MD and higher FA of the  $\mathbf{D}$  tensor than a spin-echo sequence<sup>28</sup>. For respiratory motion, a multiple breath-hold approach has been reported to be more robust in in vivo cardiac diffusion tensor parameter estimation than a navigator-based mode<sup>22</sup>. In addition, sequences with velocity (first-order motion, M1) or acceleration (second-order motion, M2) compensated diffusion gradients, that may to some extent reduce heartbeat and breathing motion artifacts, have been shown to give different measurements for pseudo-diffusion parameters (i.e.,  $f$  and  $D^*$ ) than those without compensation in IVIM studies<sup>29,30</sup>. However, it should be noted that not all acquisition strategies are suitable for IVIM tensor imaging even if some of them have been demonstrated to be capable of producing cardiac DW images with acceptable SNR. In terms of STEAM, the spoiler gradients that are used to crush the gradient echo from the third radiofrequency pulse impart a small diffusion weighting to the reference image, which means that the reference  $b$ -value is not  $0 \text{ s/mm}^2$  but a relatively low value (approximately  $15 \text{ s/mm}^2$ )<sup>20</sup>. The absence of  $b$ -values between  $0\sim 15 \text{ s/mm}^2$  could cause underestimation of pseudo-diffusion related parameters<sup>31</sup>. M1/M2 compensated diffusion gradients can minimize the effect of cardiac strain and bulk motions on DW signal attenuation, but at the same time, also compensate for coherent motion of spins in anisotropic capillaries. As a result, the majority of capillary flows in myocardial tissue could not be detected by IVIM tensor imaging with M1/M2 compensation<sup>30</sup>. With regard to breath-hold mode, while it is an effective way to avoid respiratory artifact, it frequently cannot be supported by subjects, particularly in lengthy multi-directional and multi- $b$ -values acquisitions,.

The fitting procedure is a key factor affecting IVIM parameter estimation. The most common approach to obtain IVIM parameters is the nonlinear least squares (LSQ) method based on the Levenberg-Marquardt algorithm or similar ones, but it often causes bias errors and has relatively poor measurement repeatability<sup>32</sup>. Conversely, the BSP method, which maximizes a posterior probability of IVIM parameters given the observed signals, has shown substantially smaller estimation uncertainty than the LSQ method in IVIM studies<sup>25,33</sup>. Moreover, in the work by Spinner et al. regarding in vivo cardiac scalar IVIM imaging, the BSP method resulted in higher measurement repeatability compared with LSQ<sup>29</sup>. Thus, the BSP method was used in the present study to estimate the IVIM parameters.

Both present and previous studies gave satisfactory inter-observer agreement and test-retest repeatability for FA, MD and HA of  $\mathbf{D}$  tensor although the comparison between the

present study and the literature is not straightforward owing to the variety of metrics <sup>22</sup>, which to some extent implies clinical validity of these indexes. The repeatability analysis for HA of  $\mathbf{D}$  tensor was performed for three myocardial layers and confirm prior findings that myocyte orientation in the LV wall shows transmural evolution from left-handed in the epicardium, to near perpendicular to the imaging slice in the mesocardium, to right-handed in the endocardium <sup>34</sup>. Note that WCVs of HA in mesocardium were not calculated because the mean HA value is approximately zero. The transmural evolution was not observed for HA of  $\mathbf{f}_p$  and  $\mathbf{D}^*$  tensors, either in previous research <sup>19</sup> or in the present work (Supplemental Figure 1), even though myocardial fibers and capillaries are basically aligned in histology. This may be due to fiber merging/dividing and capillary cross-connection. Therefore, the repeatability of HA of  $\mathbf{f}_p$  and  $\mathbf{D}^*$  tensors was not analyzed in the present study.

Although there are no previous reports on the measurement repeatability of pseudo-diffusion tensor ( $\mathbf{f}_p$  and  $\mathbf{D}^*$ ) indexes, the reliability and variability of scalar pseudo-diffusion parameters ( $f$  and  $D^*$ ) derived from the scalar IVIM model have been investigated in many organs, including the in vivo human heart <sup>21,29</sup>. From Eqs. (1) and (2), it can be observed that the scalar IVIM parameters are actually the projections of the corresponding tensors in the diffusion-encoding directions and could be used to calculate tensor elements. Accordingly, it could reasonably be inferred that there is certain correlation between scalar IVIM parameters and IVIM tensor indexes with regard to their measurement repeatability. Indeed, both Spinner et al. and Moulin et al. reported higher repeatability for  $f$  compared to  $D^*$ , which was consistent with our findings that  $\mathbf{f}_p$  tensor indexes were highly repeatable whereas  $\mathbf{D}^*$  tensor indexes exhibited relatively poor repeatability. However, WCVs of  $\mathbf{f}_p$  and  $\mathbf{D}^*$  tensor indexes were significantly lower (ie repeatability was higher) than those of  $f$  and  $D^*$  given by Spinner et al. This is possibly because the short time interval between the two scans in the present work eliminated the impact of some potential factors on repeatability analysis.

## Limitations

First, the sample size was relatively small and confined to a single center, preventing us from generalizing our results to a large population and other centers. However, this is an important step before further clinical application and promotion of the method. Second, the time interval between test and retest was relatively short, which limits the ability to evaluate all potential factors of variability and minimizes the effects of other variables. Third, the number of diffusion-encoding gradient directions defined in the present work only met the minimum requirement (six directions) of tensor imaging. More directions could give more accurate estimations of tensor elements, but also implies longer scan time, especially for multi- $b$ -values acquisition. The final limitation is the lack of results from other cardiac phases. It is interesting to compare the repeatability of IVIM tensor indexes between different cardiac phases in the future work.

## Conclusion

This study explored the reliability and robustness of IVIM tensor indexes in in vivo human hearts. This is an important step forward towards the clinical use of cardiac IVIM tensor imaging.  $\mathbf{D}$  and  $\mathbf{f}_p$  tensor indexes could be potential imaging biomarkers for cardiovascular characterization, disease prediction and treatment response evaluation given their satisfactory measurement repeatability. But further optimization for acquisition strategies would be needed to improve the test-retest repeatability of  $\mathbf{D}^*$  tensor indexes.



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TABLE 1 Inter-observer repeatability of FA and MD/MF of IVIM tensors at the median values in the in vivo human heart

|           |                 | FA            |               |               | <i>P</i> -value | MD ( $\times 10^{-3}$ mm <sup>2</sup> /s)/MF |               |               | <i>P</i> -value |
|-----------|-----------------|---------------|---------------|---------------|-----------------|--|---------------|---------------|-----------------|
|           |                 | Lateral       | Anterior      | Septum        |                 | Lateral                                      | Anterior      | Septum        |                 |
| <b>D</b>  | Observer I      | 0.38±0.04     | 0.38±0.03     | 0.37±0.02     | 0.601           | 1.76±0.07                                    | 1.73±0.08     | 1.73±0.07     | 0.677           |
|           | Observer II     | 0.37±0.03     | 0.36±0.03     | 0.37±0.02     | 0.783           | 1.76±0.07                                    | 1.74±0.07     | 1.72±0.07     | 0.425           |
|           | <i>P</i> -value | 0.297         | 0.520         | 0.811         |                 | 0.422  | 0.535         | 0.670         |                 |
|           | ICC             | 0.861         | 0.914         | 0.840         |                 | 0.892  | 0.916         | 0.930         |                 |
|           |                 | (0.560-0.963) | (0.704-0.978) | (0.473-0.958) |                 | (0.642-0.972)                                | (0.709-0.978) | (0.750-0.982) |                 |
|           | WCV             | 3.24%         | 2.72%         | 2.38%         |                 | 1.41%  | 1.36%         | 1.13%         |                 |
| <b>f</b>  | Observer I      | 0.44±0.04     | 0.44±0.04     | 0.44±0.03     |                 | 0.21±0.03                                    | 0.22±0.04     | 0.21±0.04     | 0.666           |
|           | Observer II     | 0.44±0.03     | 0.43±0.03     | 0.44±0.03     |                 | 0.21±0.03                                    | 0.22±0.04     | 0.22±0.03     | 0.741           |
|           | <i>P</i> -value | 0.565         | 0.398         | 0.743         |                 | 0.853  | 0.415         | 0.095         |                 |
|           | ICC             | 0.837         | 0.818         | 0.842         |                 | 0.890  | 0.851         | 0.904         |                 |
|           |                 | (0.481-0.957) | (0.454-0.951) | (0.482-0.958) |                 | (0.614-0.972)                                | (0.530-0.960) | (0.639-0.976) |                 |
|           | WCV             | 3.25%         | 3.24%         | 2.86%         |                 | 4.96%  | 7.96%         | 6.34%         |                 |
| <b>D*</b> | Observer I      | 0.64±0.08     | 0.64±0.07     | 0.65±0.05     | 0.901           | 112.31±25.62                                 | 115.86±21.45  | 110.57±21.70  | 0.884           |
|           | Observer II     | 0.63±0.10     | 0.63±0.08     | 0.64±0.06     | 0.442           | 108.46±17.70                                 | 113.61±15.47  | 110.51±14.35  | 0.825           |
|           | <i>P</i> -value | 0.784         | 0.341         | 0.462         |                 | 0.384  | 0.528         | 0.987         |                 |
|           | ICC             | 0.889         | 0.839         | 0.822         |                 | 0.860  | 0.856         | 0.856         |                 |
|           |                 | (0.615-0.971) | (0.502-0.957) | (0.452-0.952) |                 | (0.556-0.963)                                | (0.535-0.962) | (0.514-0.962) |                 |
|           | WCV             | 4.93%         | 5.37%         | 3.77%         |                 | 7.26%  | 6.24%         | 7.26%         |                 |

FA, fractional anisotropy; MD, mean diffusivity; MF, mean fraction; ICC, intraclass correlation coefficient; WCV, within coefficient of variation.

TABLE 2 Inter-observer repeatability of HA of **D** tensor at the median values in the in vivo human heart

| HA (°) of<br><b>D</b> tensor | Endocardium         | Mesocardium         | Epicardium          | <i>P</i> -value |
|------------------------------|---------------------|---------------------|---------------------|-----------------|
| Observer I                   | 32.59±4.37          | 3.57±0.78           | -27.01±4.99         | <0.05           |
| Observer II                  | 32.85±3.65          | 3.40±0.98           | -27.70±5.56         | <0.05           |
| <i>P</i> -value              | 0.329               | 0.385               | 0.499               |                 |
| ICC                          | 0.807 (0.426-0.948) | 0.818 (0.447-0.951) | 0.852 (0.525-0.961) |                 |
| WCV                          | 5.53%               | --                  | 8.22%               |                 |

HA, helix angle; ICC, intraclass correlation coefficient; WCV, within coefficient of variation.

The WCV of mesocardium was not calculated for HA, see text for details.

TABLE 3 Test-Retest repeatability of FA and MD/MF of IVIM tensors at the median values in the in vivo human heart

|           |                 | FA             |                |                | <i>P</i> -value | MD ( $\times 10^{-3}$ mm <sup>2</sup> /s)/MF |                |                | <i>P</i> -value |
|-----------|-----------------|----------------|----------------|----------------|-----------------|--|----------------|----------------|-----------------|
|           |                 | Lateral        | Anterior       | Septum         |                 | Lateral                                      | Anterior       | Septum         |                 |
| <b>D</b>  | Test            | 0.37±0.05      | 0.38±0.04      | 0.36±0.03      | 0.601           | 1.75±0.07                                    | 1.73±0.05      | 1.74±0.06      | 0.677           |
|           | Retest          | 0.39±0.04      | 0.37±0.03      | 0.36±0.02      | 0.282           | 1.74±0.06                                    | 1.74±0.06      | 1.73±0.07      | 0.895           |
|           | <i>P</i> -value | 0.489          | 0.363          | 0.260          |                 | 0.405  | 0.392          | 0.651          |                 |
|           | ICC             | 0.768          | 0.752          | 0.766          |                 | 0.873  | 0.875          | 0.869          |                 |
|           |                 | (0.321-0.973)  | (0.300-0.931)  | (0.338-0.975)  |                 | (0.588-0.966)                                | (0.595-0.963)  | (0.564-0.966)  |                 |
|           | WCV             | 4.81%          | 4.56%          | 3.16%          |                 | 1.44%  | 1.58%          | 1.59%          |                 |
| <b>f</b>  | Test            | 0.44±0.05      | 0.44±0.02      | 0.45±0.03      | 0.952           | 0.21±0.02                                    | 0.23±0.04      | 0.21±0.03      | 0.666           |
|           | Retest          | 0.44±0.03      | 0.44±0.03      | 0.44±0.03      | 0.934           | 0.20±0.02                                    | 0.22±0.04      | 0.22±0.04      | 0.484           |
|           | <i>P</i> -value | 0.798          | 0.318          | 0.439          |                 | 0.427  | 0.971          | 0.406          |                 |
|           | ICC             | 0.780          | 0.757          | 0.753          |                 | 0.811  | 0.806          | 0.808          |                 |
|           |                 | (0.322-0.941)  | (0.316-0.933)  | (0.259-0.933)  |                 | (0.427-0.949)                                | (0.381-0.949)  | (0.423-0.948)  |                 |
|           | WCV             | 3.72%          | 3.89%          | 3.78%          |                 | 7.06%  | 9.99%          | 9.88%          |                 |
| <b>D*</b> | Test            | 0.63±0.08      | 0.64±0.08      | 0.66±0.06      | 0.901           | 113.24±21.39                                 | 116.11±23.67   | 112.07±22.52   | 0.884           |
|           | Retest          | 0.62±0.05      | 0.62±0.04      | 0.64±0.07      | 0.684           | 110.75±12.17                                 | 110.71±19.60   | 107.70±17.70   | 0.900           |
|           | <i>P</i> -value | 0.380          | 0.235          | 0.505          |                 | 0.814  | 0.449          | 0.661          |                 |
|           | ICC             | 0.504          | 0.461          | 0.454          |                 | 0.555  | 0.560          | 0.517          |                 |
|           |                 | (-0.122-0.847) | (-0.136-0.827) | (-0.217-0.831) |                 | (-0.114-0.870)                               | (-0.058-0.869) | (-0.157-0.855) |                 |
|           | WCV             | 7.83%          | 7.04%          | 7.49%          |                 | 11.86%                                       | 13.12%         | 11.55%         |                 |

FA, fractional anisotropy; MD, mean diffusivity; MF, mean fraction; ICC, intraclass correlation coefficient; WCV, within coefficient of variation.

TABLE 4 Test-Retest repeatability of HA of **D** tensor at the median values in the in vivo human heart

| HA (°) of<br><b>D</b> tensor | Endocardium         | Mesocardium         | Epicardium          | <i>P</i> -value |
|------------------------------|---------------------|---------------------|---------------------|-----------------|
| Test                         | 33.38±4.52          | 3.61±0.82           | -27.36±4.51         | <0.05           |
| Retest                       | 32.05±2.80          | 3.60±0.76           | -26.05±3.15         | <0.05           |
| <i>P</i> -value              | 0.536               | 0.859               | 0.615               |                 |
| ICC                          | 0.773 (0.328-0.938) | 0.785 (0.366-0.941) | 0.765 (0.300-0.936) |                 |
| WCV                          | 5.89%               | --                  | 7.61%               |                 |

HA, helix angle; ICC, intraclass correlation coefficient; WCV, within coefficient of variation.

The WCV of mesocardium was not calculated for HA, see text for details.

FIGURE 1 Plots of SNR as a function of  $b$ -value for four equal angle segments on test (a) and retest (b).

FIGURE 2 Bland–Altman plots showing test-retest repeatability of FA and MD/MF of IVIM tensors in the lateral segment. The x-axes show the mean values of both scans and the y-axes the differences between test-retest values. Solid lines = mean absolute differences (bias). Dashed lines = 95% limits of agreement.

FIGURE 3 Bland–Altman plots showing test-retest repeatability of FA and MD/MF of IVIM tensors in the anterior segment. The x-axes show the mean values of both scans and the y-axes the differences between test-retest values. Solid lines = mean absolute differences (bias). Dashed lines = 95% limits of agreement.

FIGURE 4 Bland–Altman plots showing test-retest repeatability of FA and MD/MF of IVIM tensors in the septal segment. The x-axes show the mean values of both scans and the y-axes the differences between test-retest values. Solid lines = mean absolute differences (bias). Dashed lines = 95% limits of agreement.

FIGURE 5 Bland–Altman plots showing test-retest repeatability of HA of  $\mathbf{D}$  tensor in three myocardial layers. The x-axes show the mean values of both scans and the y-axes the differences between test-retest values. Solid lines = mean absolute differences (bias). Dashed lines = 95% limits of agreement.

FIGURE 6 FA and MD/MF maps of IVIM tensors as well as HA maps of  $\mathbf{D}$  tensor from a typical subject on test and retest.

Supplemental FIGURE 1 3D visualization of IVIM tensor fields in Fig. 6. All the IVIM tensors were represented by color-coded superquadric glyphs. The color and orientation/shape of the glyphs are determined by the HA and the eigensystem of tensor, respectively. 3D visualization of tensor information was performed using MATLAB (v. R2014a, MathWorks, Natick, MA) and Paraview (v. 4.3.1 64-bits Kitware, NM).