Intravoxel Incoherent Motion and Dynamic Contrast-Enhanced Magnetic Resonance Imaging to Early Detect Tissue Injury and Microcirculation Alteration in Hepatic Injury Induced by Intestinal Ischemia–Reperfusion in a Rat Model

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Background: Intravoxel incoherent motion (IVIM) can provide quantitative information about water diffusion and perfusion that can be used to evaluate hepatic injury, but it has not been studied in hepatic injury induced by intestinal ischemia–reperfusion (IIR). Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) can provide perfusion data, but it is unclear whether it can provide useful information for assessing hepatic injury induced by IIR.

Purpose: To examine whether IVIM and DCE-MRI can detect early IIR-induced hepatic changes, and to evaluate the relationship between IVIM and DCE-derived parameters and biochemical indicators and histological scores.

Study Type: Prospective pre-clinical study.

Population: Forty-two male Sprague–Dawley rats.

Field Strength/Sequence: IVIM-diffusion-weighted imaging (DWI) using diffusion-weighted echo-planar imaging sequence and DCE-MRI using fast spoiled gradient recalled-based sequence at 3.0 T.

Assessment: All rats were randomly divided into the control group (Sham), the simple ischemia group, the ischemia–reperfusion (IR) group (IR1h, IR2h, IR3h, and IR4h) in a model of secondary hepatic injury caused by IIR, and IIR was induced by clamping the superior mesenteric artery for 60 minutes and then removing the vascular clamp. Advanced Workstation (AW) 4.6 was used to calculate the imaging parameters (apparent diffusion coefficient [ADC], true diffusion coefficient [D], perfusion-related diffusion [D*] and volume fraction [f]) of IVIM. OmniKinetics (OK) software was used to calculate the DCE imaging parameters (Ktrans, Kep, and Ve). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were analyzed with an automatic biochemical analyzer. Superoxide dismutase (SOD) activity was assessed using the nitro-blue tetrazolium method. Malondialdehyde (MDA) was determined by thiobarbituric acid colorimetry. Histopathology was performed with hematoxylin and eosin staining.

Statistical Tests: One-way analysis of variance (ANOVA) and Bonferroni post-hoc tests were used to analyze the imaging parameters and biochemical indicators among the different groups. Pearson correlation analysis was applied to determine the correlation between imaging parameters and biochemical indicators or histological score.

Results: ALT and MDA reached peak levels at IR4h, while SOD reached the minimum level at IR4h (all P < 0.05). ADC, D, D*, and f gradually decreased as reperfusion continued, and Ktrans and Ve gradually increased (all P < 0.05). The degrees of change for f and Ve were greater than those of other imaging parameters at IR1h (all P < 0.05). All groups showed good correlation between imaging parameters and biochemical indicators and histological score.

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groups showed poor or no correlation between the imaging parameters and SOD and MDA (P [Ktrans and MDA] = 0.050, $P$ [D and SOD] = 0.125, $P$ [the remaining imaging parameters] < 0.05). All groups showed a positive correlation between histological score and Ktrans and Ve ($r = 0.775, 0.874, \text{all } P < 0.05$), and a negative correlation between histological score and ADC, D, f, and $D'$ ($r = -0.739, -0.821, -0.868, -0.841$, respectively; all $P < 0.05$). For the IR groups, there was a positive correlation between histological score and Ktrans and Ve ($r = 0.747, 0.802, \text{all } P < 0.05$), and a negative correlation between histological score and ADC, D, f, and $D'$ ($r = -0.567, -0.712, -0.715, -0.779$, respectively; all $P < 0.05$).

**Data Conclusion:** The combined application of IVIM and DCE-MRI has the potential to be used as an imaging tool for monitoring IIR-induced hepatic histopathology.

**Level of Evidence:** 1  
**Technical Efficacy Stage:** 2  

**Materials and Methods**

**Animals**

Forty-two male Sprague–Dawley (SD) rats weighing 200–250 g were acquired from the animal experiment center. The rats were randomly divided into six groups: treated with ischemic reperfusion lasting 1 hour (IR1h), ischemic reperfusion lasting 2 hours (IR2h), ischemic reperfusion lasting 3 hours (IR3h), ischemic reperfusion lasting 4 hours (IR4h), a control group (Sham), and a group treated with simple ischemic treatment lasting 1 hour (I1h) ($N = 7$ rats per group). They were placed on a homeothermic cushion to maintain body temperature. The rats were fasted from food for 12 hours before the operation. Surgery was performed under anesthesia, which was induced by injecting 5% chloral hydrate via the abdomen. IIR was induced by clamping the superior mesenteric artery for 60 minutes with a nontraumatic vascular clamp and then removing the vascular clamp for 1 hour, 2 hours, 3 hours, or 4 hours, or by only tightening the superior mesenteric artery for 1 hour using the surgical suture according to the method outlined by Kim et al. The control group underwent laparotomy and mesentery dissection only.

**Magnetic Resonance Imaging Protocol**

All examinations were performed using a 3 T scanner (Discovery 750 W, GE Healthcare, USA) with a surface soft coil (GE Healthcare, USA). To minimize the respiration motion artifact, in addition to the application of anesthesia, an abdominal belt was used for each rat in the MRI experiment. With these procedures, the breath patterns of all experimental rats were consistent during the experiment. Each rat was placed in the scanner head first and supine.

The imaging protocol comprised axial $T_2$-weighted fast spin echo (FSE) images (2D, repetition time [TR]/echo time [TE] = 5536/56 msec, slice thickness = 2 mm, field of view [FOV] = 80 × 80 mm², matrix = 160 × 160), coronal $T_2$-weighted FSE images (TR/TE = 8.9/1.1 msec, slice thickness = 2 mm, FOV = 90 × 55 mm², matrix = 160 × 160), coronal $T_2$-weighted FSE images (TR/TE = 3572/71 msec, slice thickness = 2 mm, FOV = 90 × 55 mm², matrix = 160 × 160), axial IVIM DWI (TR/TE = 3183/76 msec, slice thickness = 2 mm, FOV = 80 × 80 mm², matrix = 160 × 160), 9 $b$-values = 20, 40, 60, 80, 100, 150, 200, 500, and 800 s/mm² acceleration factor [array spatial sensitivity encoding technique] = 2) and coronal DCE (fast spoiled gradient recalled based sequence, TR/TE = 8.9/1.2 msec, slice thickness = 2 mm, acceleration factor = 2, FA = 12°, FOV = 90 × 55 mm², matrix = 160 × 160, the time resolution was 8 s for a total of 45 time points).
Intravoxel Incoherent Motion Diffusion-Weighted MRI Analysis

IVIM-DWI data were processed by using Advanced Workstation (AW 4.6) (GE Healthcare). The nonlinear least-squares curve fittings by means of the Levenberg–Marquardt method were performed using a biexponential model of 9 $b$-values to acquire the $D$, $D^*$, and $f$ values according to the following equation:

$$S_b/S_0 = (1-f) \cdot \exp(-b \cdot D) + f \cdot \exp(-b \cdot D^*).$$  \hspace{1cm} (1)
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$S_b$ represents the signal intensity at the $b$-value of 0, and $S_h$ expressed signal intensity at the specific $b$-value. $D$ represents the true diffusion as reflected by pure water-molecular diffusion. $D^*$ represents the pseudo-diffusion related to perfusion. $f$ represents the perfusion fraction reflected as a fractional volume of microcirculation within a voxel.

The ADC value was calculated by the monoexponential model, using the following equation:

$$S_h/S_0 = \exp(-b\text{ADC}).$$

Dynamic Contrast-Enhanced MRI Analysis

DCE-MRI data were imported into OmniKinetics (OK) software for processing (GE Pharmaceutical). Three quantitative pharmacokinetic DCE-MRI parameters ($K^{\text{trans}}$, $K_{ep}$, and $V_e$) were acquired using the improved Tofts–Kermode two-compartment model (Fig. 1).

### TABLE 1. Intraobserver and Interobserver Agreement in Measurements

| Measurements | Intraobserver | Interobserver |
|--------------|--------------|--------------|
| ADC          | 0.930* (0.910–0.945) | 0.959a (0.947–0.968) |
| $D^*$        | 0.969a (0.960–0.976) | 0.945a (0.931–0.957) |
| $D^f$        | 0.973a (0.965–0.979) | 0.924a (0.904–0.940) |
| $f$          | 0.941* (0.924–0.954) | 0.927a (0.907–0.943) |
| $K^{\text{trans}}$ | 0.949a (0.935–0.960) | 0.912a (0.888–0.930) |
| $K_{ep}$     | 0.842a (0.801–0.874) | 0.805a (0.739–0.853) |
| $V_e$        | 0.968a (0.959–0.975) | 0.938a (0.921–0.951) |

*Excellent agreement with intraclass correlation coefficient >0.75.

Biochemical Assessment and Histological Analysis

This prospective study was approved by the Institutional Review Board of Changzhou Second People’s Hospital. After MRI scanning, 6 mL blood was collected from the inferior vena cava of the rats to obtain serum. The levels of ALT and AST were measured by an automatic biochemical analyzer (Cobas 8000, Roche). The rats were killed to collect the left lateral lobe of liver to assess malondialdehyde (MDA) and superoxide dismutase (SOD). SOD activity was assayed using the nitro-blue tetrazolium method, as previously described by Sun et al.15 MDA was determined by thiobarbituric acid colorimetry, as previously described by Wong et al.15

The right lobe of liver was obtained after sacrifice for histological examination. The samples were immediately fixed in 5% buffered

### TABLE 2. Biochemical Indicators at Different Time Points During the Progression of Hepatic Injury

|       | N (42) | AST (U/liter) | ALT (U/liter) | MDA (nmol/mg) | SOD (U/mg) |
|-------|--------|---------------|---------------|---------------|------------|
| Sham  | 7      | 160 ± 49      | 62.5 ± 12.8   | 0.59 ± 0.08   | 367 ± 19   |
| I1h   | 7      | 158 ± 43      | 111 ± 36      | 0.67 ± 0.07   | 330 ± 23   |
| IR1h  | 7      | 184 ± 56      | 92.5 ± 45.4   | 0.70 ± 0.05*  | 323 ± 10*  |
| IR2h  | 7      | 184 ± 55      | 110 ± 23      | 0.77 ± 0.06*  | 310 ± 32*  |
| IR3h  | 7      | 190 ± 42      | 98.2 ± 30.0   | 0.77 ± 0.05*  | 319 ± 10*  |
| IR4h  | 7      | 204 ± 68      | 141 ± 29*     | 0.80 ± 0.09*  | 290 ± 39*  |
| F     |        | 0.787         | 4.834         | 10.220        | 7.358      |
| P     |        | 0.566         | 0.002         | <0.05         | <0.05      |

*$P < 0.05$ indicates statistical significance compared to the Sham group.
**TABLE 3. Intravoxel Incoherent Motion (IVIM) and Dynamic Contrast-Enhanced (DCE) Parameters at Different Time Points During the Progression of Hepatic Injury**

| Parameters | Sham | 1h | IR1h | IR2h | IR3h | IR4h | F | P |
|------------|------|----|------|------|------|------|---|---|
| N (42)     | 7    | 7  | 7    | 7    | 7    | 7    | 15.688 | <0.05 |
| ADC        | 1.70 ± 0.28 | 1.68 ± 0.28 | 1.59 ± 0.23 | 1.51 ± 0.23 | 1.43 ± 0.23 | 1.32 ± 0.21 | 38.613 | <0.05 |
| D          | 1.63 ± 0.20 | 1.62 ± 0.22 | 1.56 ± 0.24 | 1.45 ± 0.23 | 1.34 ± 0.16 | 1.12 ± 0.14 | 92.470 | <0.05 |
| D^*        | 111 ± 15  | 108 ± 23  | 105 ± 14  | 86.7 ± 14.5 | 72.8 ± 13.4 | 53.7 ± 10.6 | 224.663 | <0.05 |
| f          | 40.8 ± 1.4 | 39.9 ± 2.1 | 36.9 ± 2.0 | 35.2 ± 1.5 | 32.3 ± 1.3 | 30.3 ± 2.3 | 290.881 | <0.05 |
| K^trans    | 1.53 ± 0.27 | 1.54 ± 0.32 | 1.61 ± 0.26 | 1.80 ± 0.25 | 1.93 ± 0.22 | 1.93 ± 0.22 | 0.680  | <0.05 |
| K ep       | 4.62 ± 0.33 | 4.60 ± 0.33 | 4.59 ± 0.28 | 4.56 ± 0.28 | 4.52 ± 0.28 | 4.54 ± 0.28 | 1365.890 | <0.05 |
| V e        | 0.26 ± 0.03 | 0.27 ± 0.03 | 0.31 ± 0.03 | 0.44 ± 0.03 | 0.52 ± 0.04 | 0.71 ± 0.03 | 0.639  | <0.05 |

*P < 0.05 indicates statistical significance compared to the Sham group.

Values of ADC, D, D^*, f, K^trans, K ep, and V e expressed as means ± SDs, and compared with one-way analysis of variance and Bonferroni post-hoc test. The mean ADC, D, and D^* are expressed in ×10^{-3} mm^2/s, and f is expressed in %.

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**Statistical Analyses**

All statistical analyses were performed using SPSS 24.0 (Chicago, IL, USA) and GraphPad Prism 5.0 (San Diego, CA, USA). The intraclass correlation coefficient (ICC) was used to determine the intraobserver and interobserver agreement of IVIM and DCE parameters, with ICC >0.40 indicating fair to excellent agreement. One-way analysis of variance (ANOVA) and Bonferroni post-hoc tests were used to test the differences in imaging parameters and biochemical indicators among groups. Pearson correlation analysis was applied to determine the correlation between imaging parameters and biochemical indicators.

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**Results**

**Biochemical Indicators at Different Time Points**

- ALT and MDA reached peak levels at IR4h, and SOD reached the minimum level at IR4h (all P < 0.05).
- There was no significant difference for AST in any of the groups (P = 0.560) in Table 2.

**Correlation between Imaging Parameters and Biochemical Indicators**

- The results in Table 4 indicate that MDA was negatively correlated with ADC, D, D^*, and positively correlated with f and V e. Values showed a different trend compared to the other imaging parameters.
- The correlation between imaging parameters and biochemical indicators was determined using Pearson correlation analysis, with ICC >0.40 indicating fair to excellent agreement. One-way analysis of variance (ANOVA) and Bonferroni post-hoc tests were used to test the differences in imaging parameters and biochemical indicators among groups. Pearson correlation analysis was applied to determine the correlation between imaging parameters and biochemical indicators.

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**Conclusions**

- Intravoxel Incoherent Motion (IVIM) and Dynamic Contrast-Enhanced (DCE) parameters were successfully used to assess liver injury in this study.
- The results suggest that IVIM and DCE-MRI may be useful tools for evaluating hepatic injury.

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**Discussion**

- The study provides valuable insights into the use of IVIM and DCE-MRI for assessing hepatic injury.
- Further research is needed to validate the findings and explore the potential clinical applications of these imaging techniques.
and negatively correlated with $K_{\text{trans}}$ and $V_e$ value ($r = -0.522$ and $-0.590$, all $P < 0.05$) in all groups. Compared to all groups, the correlation between imaging parameters and MDA and SOD significantly decreased in the ischemia–reperfusion (IR) groups ($r_{[\text{ADC}]} = -0.379, 0.441$, all $P < 0.05$; $r_{[D]} = -0.446 [P = 0.05], 0.297 [P = 0.125]$; $r_{[D^*]} = -0.489, 0.441$, all $P < 0.05$; $r_{[f]} = -0.405, 0.417$, all $P < 0.05$; $r_{[K_{\text{trans}}]} = 0.374 [P = 0.050], -0.455 [P < 0.05]$; $r_{[V_e]} = 0.492, -0.422$, all $P < 0.05$).

**Pathological Progress of IIR-Induced Hepatic Injury**

The H&E staining showed a clear progressive change in the hepatic structure in Fig. 4.

**Discussion**

Recent advances have shown that IVIM promoted the application for evaluating hepatic fibrosis using quantitative parameters. Relevant DCE-MRI parameters contribute to identification of the degree of malignancy of gliomas. IVIM and DCE-MRI may be used as noninvasive methods to assess changes in diffusion, perfusion, vascular permeability, and microcirculation.
In this study, compared with the Sham group, ALT was significantly elevated in the IR4h group, and there was no significant difference in AST in any of the groups, which may indicate that AST and ALT are insufficiently sensitive to early IIR-induced liver injury. These data showed that MDA reached the peak level at IR4h, and SOD reached the minimum level at IR4h, indicating that oxidative stress occurs during IIR.

FIGURE 3: Changes in diffusion and perfusion in tissue studied by corresponding parameters in intravoxel incoherent motion (IVIM) and dynamic contrast-enhanced (DCE) magnetic resonance imaging. (a–f) Scatter plots showing the correlations between histological score and ADC value \( r = -0.739, P < 0.001 \), \( D \) value \( r = -0.821, P < 0.001 \), \( D^* \) value \( r = -0.841, P < 0.001 \), \( f \) value \( r = -0.868, P < 0.001 \), \( K^{\text{trans}} \) value \( r = 0.775, P < 0.001 \), and \( V_e \) value \( r = 0.874, P < 0.001 \) for all groups. (g–l) Scatter plots showing the correlation between histological score and ADC value \( r = -0.567, P < 0.001 \), \( D \) value \( r = -0.712, P < 0.001 \), \( D^* \) value \( r = -0.779, P < 0.001 \), \( f \) value \( r = -0.715, P < 0.001 \), \( K^{\text{trans}} \) value \( r = 0.747, P < 0.001 \), and \( V_e \) value \( r = 0.802, P < 0.001 \) for ischemia-reperfusion groups.
Furthermore, there were no significant differences in IVIM and DCE-MRI parameters in the I1h group compared with the Sham group, which implies that IIR rather than simple intestinal ischemia evoked secondary hepatic injury. The data showed that ADC and $D$ gradually decreased from the Sham group to the IR4h group. These results indicate that IIR can promote a progressive reduction in intrahepatic diffusion, which might be due to swollen hepatic cells, as confirmed in the H&E examinations at the corresponding time points. IIR might cause a release of inflammatory cytokines, leukocytes, and chemokines, which can lead to “sodium pump” inactivation for the net gain of water in the hepatocytes. In accordance with a previous study that showed that the values of $f$ and $D^*$ reduced with the aggravation of hepatic injury, this study also showed that the values $f$ and $D^*$ gradually decreased from the Sham group to the IR4h group, which indicated that these findings demonstrate a decreased blood volume and the presence of microcirculatory disorder in the liver. The H&E examinations showed that both hepatic sinusoid congestion blocking intrahepatic vessels and hepatocyte edema degeneration compressing intrahepatic vessels caused the changes in $f$ and $D^*$. Moreover, the data showed that the $K_{trans}$ value gradually increased from the Sham group to the IR4h group. An increased $K_{trans}$ implies the increase in vascular permeability, related to vascular endothelial cell injury by inflammatory cytokines, activated Kupffer cells, increased ROS, and reduced nitric oxide (NO). This study showed that the $V_e$ value gradually increased from the Sham group to the IR4h group, indicating an expansion of the EES volume. This phenomenon is considered to be mainly related to hepatocellular necrosis and vacuolization, as demonstrated by H&E examinations. This study showed that the degrees of change in $f$ and $V_e$ were higher than those of other imaging parameters at 2 hours (IR1h), which implied that perfusion plays a more important role in early hepatic injury induced by IIR. Regrettably, in the present study, the $K_{ep}$ value did not reduce significantly with prolonged reperfusion time, although it did show a declining tendency. This lack of significance is likely due to an insufficient reperfusion time and minor sample size.

The data also revealed that MDA was negatively correlated with ADC, $D$, $D^*$, and $f$, and positively correlated with $K_{trans}$ and $V_e$ value in all groups. Meanwhile, SOD was...
positively correlated with ADC, $D$, $D^*$, and $f$, and negatively correlated with $K^{\text{trans}}$ or $V_e$ in all groups. However, the correlation between imaging parameters and MDA and SOD was poor for the IR groups. The change in imaging parameters suggests the existence of cellular oxidative stress injury, but it has limited ability to demonstrate the tendency for variations of these parameters during reperfusion. Moreover, there was a significantly positive correlation between histological score and $K^{\text{trans}}$ and $V_e$, and a significantly negative correlation between histological score and ADC, $D$, $f$, and $D^*$ in all groups and only IR groups, which probably contributed to assessing the degree of damage in hepatic parenchyma. Furthermore, the correlation between $D^*$ and histological score was higher than that between ADC and $D$ and histological score, which implied that compared with the diffusion parameters, the perfusion parameters are more sensitive to IIR-induced hepatic injury, which are crucial factors for evaluating hepatic dysfunction.24,30

**Limitations**

This study has several limitations. First, while selecting the ROI, we only measured the right lobe of the liver in order to maintain consistency with the pathological samples and reduce heartbeat artifacts. However, this method might fail to reflect the overall liver damage. Second, the sample size was small, and the reperfusion time was short. Thus, it was difficult to observe overall changes of hepatic injury and biochemical indicators, mainly due to the higher mortality rate of rats with a prolonged intestinal reperfusion time.

**Conclusion**

This study demonstrated that IVIM and DCE-MRI can non-invasively estimate hepatic pathophysiological processes in a rat IIR-induced hepatic injury model. The change in microcirculation and perfusion seemed to be the major factors in IIR-induced hepatic injury. Third, $f$, $D^*$, and $V_e$ were more sensitive for histological change, which implies that IVIM and DCE-MRI might provide effective parameters in the process of IIR-induced hepatic injury.

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