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***Basic Study***

**Novel rat model of heterogeneous hepatic injury by colchicine splenic vein injection**

Zhang Y *et al*. Establishment of a novel rat model

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**Abstract**

***AIM***

To establish a novel rat model of heterogeneous hepatic injury.

***METHODS***

Seventy male Sprague-Dawley rats were randomly divided into a colchicine group (*n* = 60) and a control group (*n* = 10). A 0.25% colchicine solution (0.4 mL/kg) was injected *via* the splenic vein to the colchicine group in order to develop a rat model of heterogeneous hepatic injury. An equal volume of normal saline was injected *via* the splenic vein in the control group. After the operation, at least 7 rats of the colchicine group were selected randomly for magnetic resonance imaging (MRI) examination at d 3, 7 and 14 and wk 4 , 8 and 12. Each rat was euthanized after the MRI examination. The 10 rats of the control group underwent MRI examinations at the same time points, and were euthanized at the 12th wk after the MRI examinations. T2-weighted image (T2WI) and diffusion-weighted imaging (DWI) were used to evaluate the heterogeneous hepatic injury. Injury between the left and right hepatic lobes was assessed on liver sections according to the histological scoring criteria, and then correlated with the result of MRI study.

***RESULTS***

Obvious pathological change occurred in the hepatic parenchyma of the colchicine group. The hepatic injury score was significantly different between left and right lobes at each time point respectively (*P* < 0.05). Meanwhile, there were significant differences in the apparent diffusion coefficients of DWI (d 3: 0.110 ± 0.121 *vs* -0.001 ± 0.005; wk 1: 0.091 ± 0.027 *vs* 0.010 ± 0.010; wk 2: 0.234 ± 0.087 *vs* 0.009 ± 0.011; wk 4: 0.171 ± 0.053 *vs* 0.011 ± 0.008; wk 8: 0.173 ± 0.058 *vs* 0.035 ± 0.022; wk 12: 0.190 ± 0.078 *vs* 0.021 ± 0.011) and liver-to-muscle ratio on T2WI (d 3: 0.85 ± 0.045 *vs* 0.016 ± 0.011; wk 1: 0.067 ± 0.015 *vs* 0.007 ± 0.004; wk 2: 0.081 ± 0.027 *vs* 0.008 ± 0.006; wk 4: 0.110 ± 0.062 *vs* 0.007 ± 0.005; wk 8: 0.090 ± 0.040 *vs* 0.006 ± 0.007; wk 12: 0.092 ± 0.046 *vs* 0.007 ± 0.005) between the left and right lobes in the colchicine group (*P* < 0.05) at each time point respectively, and similar differences were seen between the colchicine group and the control group. Finally, there was a significant correlation between hepatic injury score and the apparent diffusion coefficient value (*r* = -0.682, *P* = 0.000) and the liver-to-muscle ratio (*r* = -0.245, *P* = 0.018).

***CONCLUSION***

Colchicine injection *via* splenic vein successfully develops a heterogeneous hepatic injury model in rat. DWI and T2WI may help evaluate the heterogeneous injury among liver lobes.

**Key words:** Heterogeneous hepatic injury; Rat model; Colchicine; T2WI; DWI

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**Core tip:** In this article, the injection of colchicine through splenic vein is shown to develop a rat model of heterogeneous hepatic injury successfully. The colchicine injection led to obvious pathological change of hepatic parenchyma over time, and induced significant differences in the left and right lobes, as evidenced by liver injury score, apparent diffusion coefficient value, and liver-to-muscle ratio of T2-weighted images at each time point. Data generated using this model suggested that diffusion-weighted imaging and T2-weighted images can be used to evaluate the heterogeneous injury among liver lobes.

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**INTRODUCTION**

Heterogeneous hepatic injury is often manifested in patients with hepatic tumors, especially involving those with hepatitis and cirrhosis. Clinical estimation of total and regional hepatic function is essential for preventing postoperative liver failure and devising an effective treatment plan for patients with hepatic tumor[1]. The current technological limitations that preclude whole-organ assessment of heterogeneous hepatic injury present a clinical challenge. Unfortunately, the lack of an ideal animal model of heterogeneous hepatic injury has hindered the development of such assessment methods[2]. The establishment of a practical and reproducible animal model of heterogeneous hepatic injury is urgently needed to provide a manipulable *in vivo* tool for future development of simple, safe and effective whole liver assessment methods.

Although several animal models have been established to evaluate liver function, they are limited in their ability to reflect homogeneous hepatic injury. The most popular of these models induce hepatic injury by subcutaneous injection of a carbon tetrachloride (commonly known as CCl4) plus olive oil mixture[3] or by 4-wk consecutive daily gavage with colchicine (in mice)[4]. Colchicine is an antimitotic cytotoxic agent derived from the *Colchicum autumnale* plant.

We chose to further study the ability of colchicine to establish hepatic injury in rats (by injection through the splenic vein). Once this model was established, we sought to determine whether the consequent heterogeneous injury between the left and right hepatic lobes, assessed according to histological scoring criteria, would correlate with findings on magnetic resonance imaging (MRI), particularly the MR sequences, to evaluate hepatic injury[5-6].

**MATERIALS AND METHODS**

***Compliance with ethical requirements***

All experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. This study was approved by the animal care committee of our University.

***Animals and grouping***

Seventy male Sprague-Dawley rats of specific pathogen-free grade, weighing 280 ± 20 g, were purchased form Changsheng Laboratory in Benxi, Liaoning (Certification number: SCXK-2015­0001). Before the start of experimentation, the rats were housed in separate cages and fed a normal diet. For the study, the animals were randomly divided into a control group (*n* = 10) and a colchicine group (*n* = 60). All animals maintained the standard diet before their operations.

***Establishment of the heterogenous hepatic injury model***

All rats were fasted at least 6 hr before the operation. A 40 mg/kg dose of 1% pentobarbital sodium was injected intraperitoneally for anesthesia. For rats in the colchicine group, the peritoneal cavity was opened and a 0.4 mL/kg dose of 0.25% colchicine (> 98% purity; Nanjng Zelang Medical Technology Co. Ltd., Nanjing, China) was injected into the splenic vein at a rate of 0.1 mL/s. For rats in the control group, the peritoneal cavity was opened similarly and an equal volume of normal saline was injected *via* the splenic vein (Figure 1). After the operation, all animals were fed normal diet. Twelve rats in the colchicine group died after 24 hr and were excluded from the experiment.

***MRI procedure***

After the operation, rats of the colchicine group were randomly selected for MRI examinations under anesthesia, as follows: 7 rats on the 3rd, 7th and 14th d and in the 4th wk; and, 10 rats in the 8th and 12th wk. All rats were euthanized by anesthetic overdose following the MRI examination. Accidental anesthetic overdose caused death in one in the 8th wk and one in the 12th wk. The 10 rats of the control group underwent similar MRI examination at the same time points, and were euthanized at the 12th week after the MRI examinations. Liver tissues were resected from all euthanized rats and preserved by fixation in 4% paraformaldehyde.

Prior to the MRI examinations, the selected rats were fasted for about 8 hr. The MRI was performed using a Signa HDxt 3.0T magnetic scanner with a wrist coil (GE Healthcare, Chicago, IL, United States). The detailed scanning settings were as follows: T2-weighted image (T2WI) used TR of 3840 ms, TE of 85 ms, field of view of 14 cm, NEX of 4, matrix of 256 × 192, slice thickness of 3 mm, flip angle of 90°, and scan time of 3 min and 12 sec; diffusion-weighted imaging (DWI) used b of 500 s/mm2, TR of 5000 ms, TE of 77.3 ms, field of view of 14 cm, NEX of 2, matrix of 128 × 128, slice thickness of 3 mm, flip angle of 90°, and scan time of 40 sec.

***Image analysis***

Image analysis was performed by two radiologists working independently, each with more than 5 yr clinical experience and blinded to the histopathologic results. The largest as possible regions of interest (ROIs) were defined in both left and right lobes of the liver in three successive slices on T2WI and apparent diffusion coefficient (ADC) maps; vessels and artifacts were excluded when positioning the ROI. The signal intensities of the erector spinae muscles on T2WI were detected on the same slices simultaneously, then the average values of these measurements on the three successive slices were calculated. Based on the average values, the liver-to-muscle ratio (LMR) on T2WI, its differences on T2WI between the left and right lobes (ΔLMR) and the differences of ADC values between the left and right lobes (ΔADC) were calculated[7-8].

***Liver histopathology***

The fixed liver tissue samples were paraffin-embedded and sliced (5.0 µm). After conventional hematoxylin-eosin staining, the sections were examined with a light microscope. Masson's trichrome staining was used to assess fibrosis. Scoring for liver injury was made according to extent of hepatocellular necrosis, edema, and inflammatory cell infiltration, using the following scoring system: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The extent of liver fibrosis was scored as: 0 = no fibrosis, 1 = fibrous portal expansion, 2 = bridging fibrosis, 3 = bridging fibrosis with architectural distortion, and 4 = liver cirrhosis[9-10].

***Statistical analysis***

The data are expressed as mean ± standard deviation. Normal distribution was assessed by the Kolmogorov-Smirnov test. Differences in liver injury, ΔLMR and ΔADC were compared between the colchicine group and the control group by using the Student's *t*-test or Mann-Whitney *U*-test. Statistical significance was defined as *P* < 0.05. The correlations between LMR, ADC value and liver injury score in the colchicine group were assessed using the Spearman's rank correlation coefficient. The threshold for statistical significance was defined as *P* < 0.05.

**RESULTS**

***Postoperative status***

All animals awoke within 1 hr after the operation. Rats in the colchicine group demonstrated fatigue, reduced food and water consumption, and slow movement after the operation. Though the activity of rats in the control group was slightly decreased, their general state was normal upon awakening. All rats in the control group survived the operation, but 12 rats in the colchicine group did not survive the procedure and died within 24 hr after the operation.

***Pathology***

No obvious pathological change was apparent in the rat liver tissues of the control group under light microscope. In the colchicine group, hepatocellular necrosis, inflammatory cell infiltration, hepatocellular edema and liver fibrosis were observed, accompanied by hepatic cords disappearance and cell nuclei dissolution. On d 3 after colchicine injection, there was massive inflammatory cell infiltration and hepatocellular edema and mild liver necrosis, without apparent fibrosis. On the 14th d after injection, the inflammation had reduced and necrosis had increased, but fibrosis was still absent. At the 4th wk after injection, cholestasis and early fibrosis were observed. At the 8th and 12th wk after injection, there was further fibrosis (Figure 2). Based on the scoring criteria[9-10], the hepatic injury score was significantly different between the left and right lobes at each time point (*P* < 0.05) (Figure 3).

***Results of MRI***

Comparisons of ΔADCs in the right and left hepatic lobes of the colchicine group with those of the control group are shown in Figure 4a, and demonstrated a statistically significant difference at each time point (*P* < 0.05). Statistically significant differences were also found between the right and left hepatic lobes for the ΔLMRs from T2WIs of the colchicine group and compared to those of the control group at each time point (*P* < 0.05; Figure 4b).

***Relationships between pathology scores and MRI variables***

The relationship between the ADC value and hepatic injury score is illustrated in Figure 5a. In particular, the ADC values decreased as the hepatic injury score increased, and the correlation reached statistical significance (*r* = -0.682; *P* = 0.000). The LMR and hepatic injury score also demonstrated a statistically significant negative correlation (*r* = -0.245; *P* = 0.018) (Figure 5b).

**DISCUSSION**

Liver resection is performed on patients exhibiting heterogeneous hepatic injury induced by chemotherapy, metabolic syndrome or cirrhosis[1] [11-16], and this can lead to postoperative liver failure, which has become the leading cause of mortality after liver resection[17-19]. Assessment of the uneven distribution of hepatic function and prediction of reserved liver function are essential for preventing this postoperative liver failure[12]. Therefore, the establishment of a practical animal model of heterogeneous liver injury is necessary, as it will serve as the basis for further studies to curtail or eliminate this dire situation. Although some animal models of hepatic injury exist, including the thioacetamide-induced rats and choline-deficient diet-induced rats[20] as well as the models described in the Introduction, these models show homogeneous hepatic injury, and cannot be used to investigate the heterogeneous liver injury condition that exists in human patients.

In this study, we successfully established an animal (rat) model of heterogeneous liver injury by injection of colchicine through the splenic vein. The surgically-targeted introduction of the colchicine is necessary because of its toxicity against all cells in the body, by which it can cause multiorgan toxicity[21]. The mechanism of colchicine toxicity is based in its binding to the intracellular tubule, arresting polymerization of the alpha and beta forms into microtubules; as a consequence, proteins involved in Golgi apparatus processes, endocytosis, exocytosis, cellular shape and motility are impaired. Mitosis is also disrupted in the metaphase, according to the effects on microtubule-dependent functions at play during chromosome separation[22-23].

Colchicine has been used in past laboratory research studies to induce conspicuous hepatotoxicity diseases in animals, including liver necrosis and steatosis[4] [24]. On the other hand, clinical studies have found that colchicine in blood of the portal vein (originating from the superior mesenteric vein and the splenic vein) is unevenly distributed in different lobes of the liver (after the portal vein merge). Considering this human observation, we injected the colchicine, in this study, through the splenic vein of our rat model to introduce an inhomogenent hepatic injury⎯and successfully induced a statistically significant difference in the pathological changes between the left and right hepatic lobes. Histological analysis showed heterogeneous hepatocellular necrosis, edema, inflammatory cell infiltration and liver fibrosis, as well as cord disappearance, fibrous septa collapse and cell nuclei dissolution. These colchicine injection-related features support the notion that this rat model can be used for the further studies of hepatic injury, such as quantitative analysis of the regional liver function.

In this model, the pathological changes of hepatic parenchyma mirrored the findings of previous studies[6], namely the decreased inflammation of hepatic parenchyma development within 2 wk after the colchicine injection and the progressively irreversible development of fibrosis. The current gold standard for estimation of liver injury is the liver biopsy, yet liver specimens obtained by needle biopsy represent only a very small part of the liver parenchyma[25]. Moreover, the associated procedure-related features of sampling error, invasiveness, interobserver variability, and risk of complications make liver biopsy impractical for estimating inhomogeneous hepatic injury[26]. Finally, no serum markers or clinical signs described to date can accurately assess liver regional function[20].

Recently, several MRI methods have been developed to characterize the processes of various liver diseases and their extents (grades)[27]. In addition, several studies have confirmed the value of MR sequences for evaluating liver injury[5-6] [28]. Therefore, in this study we used the T2WI and DWI to assess the heterogeneous liver injury in our model. In DWI, ADC values quantify the diffusion of random molecular motions[29]. As such, in the early stage of chemical hepatic injury, decreased ADC values can reflect a reduced ratio of extracellular/intracellular water volume caused by cytotoxic intracellular edema, as well as decreased intracellular proton movement resulting from energy loss. As fibrosis progresses, narrowed sinusoids and restricted water mobility caused by accumulation of collagen fibers, glycosaminoglycans and proteoglycan, lead to even lower ADC values for the liver parenchyma.

The decrease in ADC values as liver disease progresses and fibrotic score increases is reported in the literature[30]. Studies have also shown hepatic injury resulting in increased T2 relaxation time and heightened T2WI sensitivity to necrosis[31]. In addition, T2WI has been shown as useful for monitoring *in vivo* hepatotoxicity over time[32]. In our study, the differences of histological changes between the left and right lobes caused by uneven injury was reflected by the LMR, calculated from the T2WI and DWI ADC values. Both the ADC value and LMR decreased as the hepatic injury score increased, and the correlations were statistically significant. The correlation coefficient between the ADC value and the hepatic injury score was significantly higher than that between the LMR and the hepatic injury score. Thus, the results of this study support the notion that both ADC value and LMR can be potentially useful for evaluating heterogeneous hepatic injury.

There are several limitations to the present study that must be considered when interpreting or generalizing our findings. Firstly, the stability of the uneven hepatic injury is influenced by individual differences of animals. Secondly, none of the MRI parameters was obtained over time to evaluate longitudinal changes. Thirdly, although the ADC value from DWI enables noninvasive prediction of heterogeneous hepatic injury, it is limited by its relatively poor spatial resolution. Further studies are needed to explore other techniques, such as gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (commonly known as Gd-EOB-DTPA)-enhanced MRI, T1 mapping and T2 mapping for assessing regional liver function in this model[28].

In summary, a novel rat model with uneven hepatic injury was established by injection of colchicine through the splenic vein. Data generated using this model suggested that DWI and T2WI can potentially evaluate heterogeneous injury between liver lobes.

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**ARTICLE HIGHLIGHTS**

***Research background***

Heterogeneous hepatic injury is often exhibited in patients who will undergo liver resection, especially in those with hepatitis and cirrhosis. Assessment of uneven hepatic function is essential for preventing postoperative liver failure. To date, there is no simple, safe and effective method to evaluate heterogeneous hepatic injury, due to the absence of an ideal animal model for use in research to develop such.

***Research motivation***

The establishment of a practical and reproducible animal model of heterogeneous hepatic injury will serve as the basis for future research that will ultimately benefit human clinical practice. In the present study, a novel rat model was established by injection of colchicine through the splenic vein, aiming to develop a practical model of heterogeneous hepatic injury. The heterogeneous injury differences between the left and right hepatic lobes was assessed using liver sections and histological scoring criteria, and the data were then correlated with magnetic resonance imaging (MRI) findings, particularly the MR sequences, for evaluating hepatic injury.

***Research objectives***

To establish a practical rat model of heterogeneous hepatic injury by injection of colchicine through the splenic vein, which can be used for further studies into human clinical parameters, such as quantitative analysis of regional liver function.

***Research methods***

Seventy male Sprague-Dawley rats were randomly divided into a colchicine group (*n* = 60) and a control group (*n* = 10). For the colchicine group, a 0.25% colchicine solution (0.4 mL/kg) was injected *via* the splenic vein to develop a rat model of heterogeneous hepatic injury. For the control group, an equal volume of normal saline was injected *via* the splenic vein. After the operation, at d 3, 7 and 14 and wk 4 , 8 and 12, more than 7 rats of the colchicine group were selected randomly for MRI examination; all rats were euthanized after the examination. The 10 rats of the control group underwent MRI examinations at the same time points, and were euthanized at the 12th wk after the MRI examinations. T2-weighted images (T2WI) and diffusion weighted imaging (DWI) were used to evaluate the heterogeneous hepatic injury. The heterogeneous injury in the left and right hepatic lobes was comparatively assessed on liver sections according to histological scoring criteria, and then correlated with the results from the MRI study.

***Research results***

The colchicine group showed obvious pathological change of hepatic parenchyma over time. Moreover, the hepatic injury scores were significantly different between the left and right lobes at each time point (*P* < 0.05). There were also significant differences in the apparent diffusion coefficients of DWI and the liver-to-muscle ratios of T2WI between the left and right lobes of the colchicine group (*P* < 0.05) at each time point, with similar differences between the colchicine group and the control group. Finally, there was significant correlation between the hepatic injury score and the apparent diffusion coefficient value (*r* = -0.682, *P* = 0.000) and the liver-to-muscle ratio (r = -0.245, *P* = 0.018). There are some issues, such as stability of the uneven hepatic injury influenced by individual differences of animals and the absence of time-related MRI parameters reflective of longitudinal changes, that remain to be addressed.

***Research conclusions***

In this study, it was found that injection of colchicine through the splenic vein can develop a rat model of heterogeneous hepatic injury successfully. The results of this study support the notion that DWI and T2WI can be used to evaluate the heterogeneous injury among liver lobes.

***Research perspectives***

This model may serve as tool for further research to explore other new techniques, such as gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (commonly known as Gd-EOB-DTPA)-enhanced MRI, T1 mapping and T2 mapping, for assessing the uneven distribution of hepatic function and predicting the reserved liver function for prevention of postoperative liver failure.

**REFERENCES**

1.**Henrik Nilsson**,Silja Karlgren,Lennart Blomqvist,Eduard Jonas.The inhomogeneous distribution of liver function: possible impact on the prediction of post-operative remnant liver function.*HPB* 2015;**17**:272–277[PMID: 25297934 DOI: 10.1111 / hpb.12348]

2.**Seyama Y**, Kokudo N. Assessment of liver function for safe hepatic resection. *Hepatol Res* 2009; **39**:107-16[PMID: 19208031 DOI: 10.1111 / j.1872-034X.2008.00441.x]

3. **Ma C**, Liu A, Wang Y, Geng X, Hao L, Song Q, Sun B, Wang H, Zhao G. The hepatocyte phase of Gd-EOB-DTPA-enhanced MRI in the evaluation of hepatic fibrosis and early liver cirrhosis in a rat model: an experimental study. *Life Sci* 2014;**108**:104-8[PMID: 24881519 DOI: 10.1016/j.lfs.2014.05.016]

4. **Guo X**, Lin D, Li W, Wang K, Peng Y, Zheng J. Electrophilicities and Protein Covalent Binding of Demethylation Metabolites of Colchicine. *Chem Res Toxicol* 2016; **29**: 296-302[PMID: 26845511 DOI: 10.1021/acs.chemrestox.5b00461]

5.**Cassinotto C**, Feldis M, Vergniol J, Mouries A, Cochet H, Lapuyade B, Hocquelet A, Juanola E, Foucher J, Laurent F, De Ledinghen V.MR relaxometry in chronic liver diseases: Comparison of T1 mapping,T2 mapping, and diffusion-weighted imaging for assessing cirrhosis diagnosis and severity. *Eur J Radiol* 2015; **84**: 1459-1465[PMID: 26032126DOI: 10.1016/j.ejrad.2015.05.019]

6.**Zhao F**, Wang YX, Yuan J, Deng M, Wong HL, Chu ES, Go MY, Teng GJ, Ahuja AT, Yu J. MR T1ρas an imaging biomarker for monitoring liver injury progression and regression:an experimental study in rats with carbon tetrachloride intoxication. *Eur Radiol* 2012; **22**: 1709-16[PMID: 22752522DOI: 10.1007/s00330-012-2419-0]

7.**Shimamoto D**, Nishie A, Asayama Y, Ushijima Y, Takayama Y, Fujita N, Shirabe K, Hida T, Kubo Y, Honda H.MR Prediction of Liver Function and Pathology Using Gd-EOB-DTPA: Effect of Liver Volume Consideration. *Biomed Res Int*2015[PMID:26609519DOI: 10.1155/2015/141853]

8.**Katsube T**, Okada M, Kumano S, Imaoka I, Kagawa Y, Hori M, Ishii K, Tanigawa N, Imai Y, Kudo M, Murakami T. Estimation of liver function using T2\* mapping on gadolinium ethoxybenzyl.*Eur J Radiol* 2012;**81**:1460-4[PMID:21514080DOI: 10.1016/j.ejrad.2011.03.073]

diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging

9.**Yu Lua**, Pengfei Liub, Peng Fua, Yaodong Chenc, Dong Nanb, Xiuhua Yang.Comparison of the DWI and Gd-EOB-DTPA-enhanced MRI on assessing the hepatic ischemia and reperfusion injury after partial hepatectomy. *Biomed Pharmacother* 2017;**86**:118–126[PMID:27951418DOI: 10.1016 / j.biopha.2016.11.123]

10.**Y. Tomimaru**, Y. Sasaki, T. Yamada et al.Fibrosis in noncancerous tissue is the unique prognostic factor for primary hepatocellular carcinoma without hepatitis B or C viral infection. *World Journal of Surgery* 2006; **30**:1729–1735[PMID:16850156 DOI: 10.1007/s00268-005-0123-9]

11. **Tsujino T,** Samarasena JB, Chang KJ. EUS anatomy of the liver segments.

*Endosc Ultrasound* 2018; **7**: 246-251[PMID: 30117487 DOI: 10.4103/eus.eus\_34\_18]

12.**Nilsson H**, Blomqvist L, Douglas L, Nordell A, Janczewska I, Näslund E, Jonas E. Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. *Br J Radiol* 2013; **86**[PMID: 23403453DOI: 10.1259/bjr.20120653]

13.**de Graaf W**, Häusler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, Kullak-Ublick GA, Hesselmann R, van Gulik TM, Stieger B.Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. *J Hepatol* 2011;**54**:738-45[PMID: 21163547DOI: 10.1016/j.jhep.2010.07.047]

14.**Arun J1**, Jhala N, Lazenby AJ, Clements R, Abrams GA.Influence of liver biopsy heterogeneity and diagnosis of nonalcoholic steatohepatitis in subjects undergoing gastric bypass. *Obes Surg* 2007; **17**: 155-61[PMID: 17476865DOI: 10.1007/s11695-007-9041-2]

15.**Merriman RB1**, Ferrell LD, Patti MG, Weston SR, Pabst MS, Aouizerat BE, Bass NM Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology* 2006; **44**: 874-80[PMID: 17006934DOI: 10.1002/hep.21346]

16.**Ratziu V1**, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T.Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-906[PMID: 15940625]

17.**Balzan S1**, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F.The ‘50-50 criteria’ on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005; **242**: 824-8[PMID: 16327492]

18.**Capussotti L**, Viganò L, Giuliante F, Ferrero A, Giovannini I, Nuzzo G.Liver dysfunction and sepsis determine operative mortality after liver resection. *Br J Surg* 2009; **96**:88-94[PMID: 19109799DOI: 10.1002/bjs.6429]

19. **Mullen JT**, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, Abdalla EK, Curley SA, Capussotti L, Clary BM, Vauthey JN.Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy.*J Am Coll Surg* 2007 ;**204**:854-62[PMID: 17481498 DOI: 10.1016/j.jamcollsurg.2006.12.032]

20. **Tsuda N**, Matsui O. Signal profile on Gd-EOB-DTPA-enhanced MR imaging in non-alcoholic steatohepatitis and liver cirrhosis induced in rats: correlation with transporter expression.*Eur Radiol* 2011;**21**:2542-50[PMID: 21830099 DOI: 10.1007/s00330-011-2228-x]

21.**Smilde BJ,** Woudstra L, Fong Hing G, Wouters D, Zeerleder S, Murk JL, van Ham M, Heymans S, Juffermans LJ, van Rossum AC, Niessen HW, Krijnen PA, Emmens RW. Colchicine aggravates coxsackievirus B3 infection in mice. *Int J Cardiol.* 2016; **216:**58-65[PMID: 27140338 DOI: 10.1016/j.ijcard.2016.04.144]

22.**Deng M**, Zhao F, Yuan J, et al. Liver T1rho MRI measurement in healthy human subjects at 3 T: a preliminary study with a twodimensional fast-field echo sequence. *Br J Radiol* 2012;**85**:590–595 [PMID: 22422392 DOI: 10.1259 / BJR / 98745548]

23.**Unal E**, Idilman IS, Karçaaltıncaba M.Multiparametric or practical quantitative liver MRI:towards millisecond, fat fraction, kilopascal and function era.*Expert Rev Gastroenterol Hepatol* 2017 ;**11**:167-182 [PMID: 27937040 DOI: 10.1080/17474124.2017.1271710]

24.**Decleves X**, Niel E, Debray M, Scherrmann JM. Is P-glycoprotein (ABCB1) a phase 0 or a phase 3 colchicine transporter depending oncolchicine exposure conditions? *Toxicol Appl Pharmacol* 2006;**217**:153–160 [PMID: 16978677DOI: 10.1016 / j.taap.2006.08.004]

25.**Fontana RJ**, Lok AS. Noninvasive monitoring of patients with chronic hepatitis C. *Hepatology* 2002;**36**:57–64 [PMID: 12407577 DOI: 10.1053/jhep.2002.3680]

26.**Kose S**, Ersan G, Tatar B, Adar P, Sengel BE. Evaluation of Percutaneous Liver Biopsy Complications in Patients with Chronic Viral Hepatitis. *Eurasian J Med* 2015;**47**: 161-4 [PMID: 26644763 DOI: 10.5152/eurasianjmed.2015.107]

27. **Wibmer A**, Nolz R, Trauner M, Ba-Ssalamah A.Functional MR imaging of the liver. *Radiologe* 2015; **55**: 1057-66 [PMID: 26610680 DOI: 10.1007/s00117-015-0032-3]

28.**Poynard T**, Lenaour G, Vaillant JC, et al. Liver biopsy analysis has a low level of performance for diagnosis of intermediate stages of fibrosis. *Clin Gastroenterol Hepatol* 2012;**10**: 657-63 [PMID: 22343514 DOI: 10.1016/j.cgh.2012.01.023]

29.**Slobodnick A**, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: old and new. *Am J Med* 2015; **128**: 461-70 [PMID: 25554368 DOI: 10.1016/j.amjmed.2014.12.010]

30. **Roubille F**, Kritikou E, Busseuil D, Barrere-Lemaire S, Tardif JC. Colchicine: an old wine in a new bottle? *Antiinflamm Antiallergy Agents Med Chem* 2013; **12**: 14-23 [PMID: 23286287]

31. **Shankar S** ，Kalra N ，Bhatia A ，Srinivasan R ，Singh P ，Dhiman RK ，Khandelwal N ，Chawla Y. Role of Diffusion Weighted Imaging (DWI) for Hepatocellular Carcinoma (HCC) Detection and its Grading on 3T MRI: A Prospective Study. *J Clin Exp Hepatol* 2016; **6**: 303-310 [PMID: 28003720 DOI: 10.1016/j.jceh.2016.08.012]

32.**Koinuma M1**, Ohashi I, Hanafusa K, Shibuya H.Apparent Diffusion Coefficient Measurements with Diffusion-Weighted Magnetic Resonance Imaging for Evaluation of Hepatic Fibrosis. *J Magn Reson Imaging* 2005;**22**:80-5 [PMID: 15971188 DOI: 10.1002/jmri.20344]

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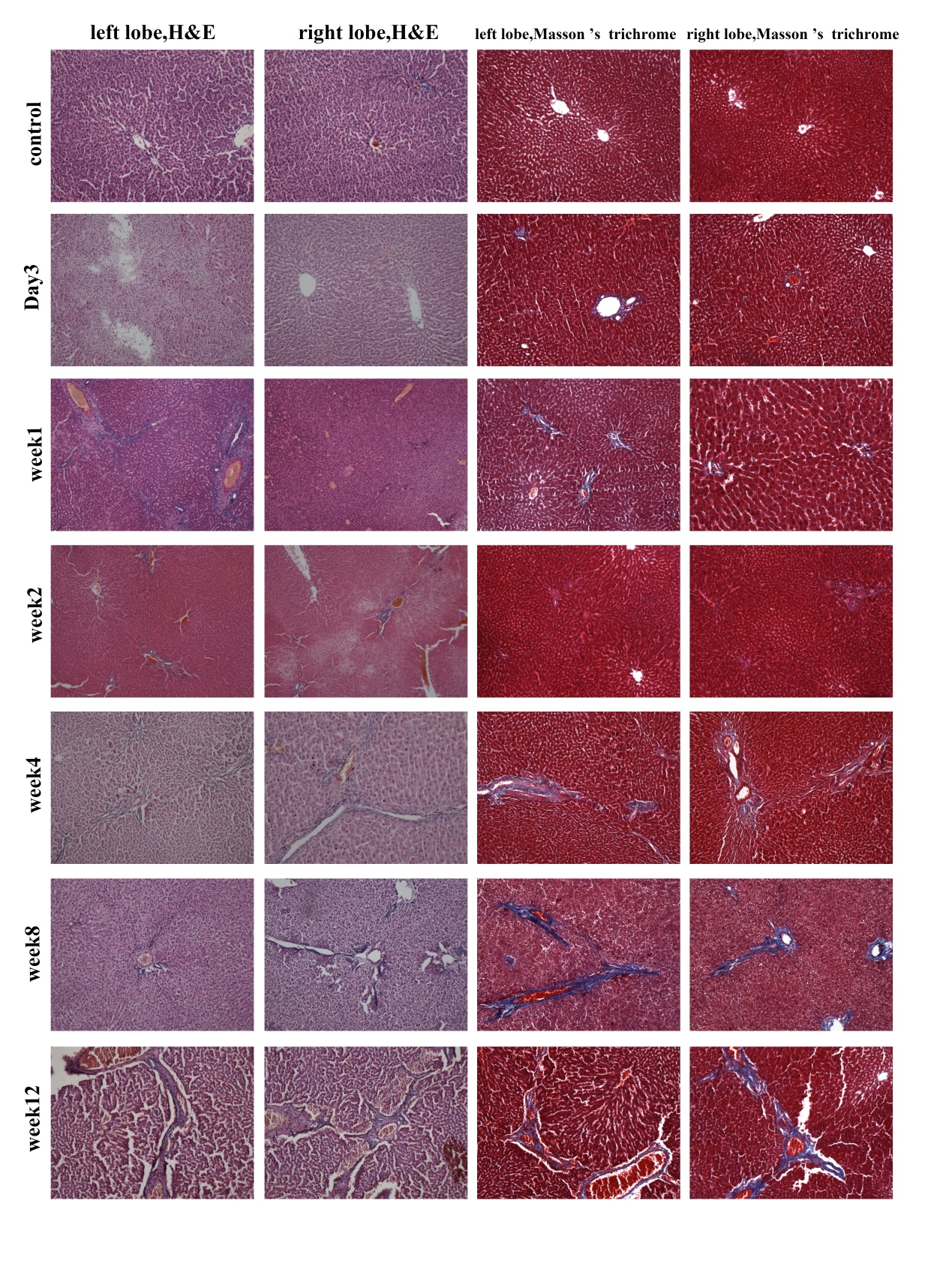
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**Figure 1** **Establishment of the rat model with heterogenous hepatic injury.** After anesthesia and splenic vein dissection, a 0.4 mL/kg dose of 0.25% colchicine was injected *via* the splenic vein.

**Figure 2** **Histopathological changes of the liver (× 100).** Hematoxylin-eosin staining on the left lobe (1st column) and right lobe (2nd column) and Masson’s trichrome staining on the left lobe (3rd column) and right lobe (4th column) is shown for the control group (1st row) and for each time point after the colchicine injection (2nd to 7th rows). No obvious pathological changes were observed in the control group. The hepatic injury in the colchicine group was different between the left and right lobes at each time point. On d 3 after the colchicine injection, there was massive inflammatory cell infiltration and hepatocellular edema, and mild liver necrosis. Then, to the 14th d, the inflammation reduced and the necrosis increased, but fibrosis remained absent. At the 4th wk, cholestasis and early fibrosis had developed. At the 8th and 12th wk, the fibrosis had progressed.



**Figure 3** **Comparisons of hepatic injury scores of the left and right liver lobes in the colchicine group at each time point.** Differences in hepatic injury between the left and right lobes reached statistical significance at each time point (*P* < 0.05).

**Figure 4 Comparisons of ΔADC (A) and ΔLMR (B) for the colchicine group *versus* the control group at each time point.** Data are expressed as mean ± standard deviation. Statistically significant differences were present (*P* < 0.05). ADC: Apparent diffusion coefficient; LMR: Liver-to-muscle ratio. ΔADC: Differences of diffusion-weighted imaging ADC values between the left and right lobes; ΔLMR: Differences of LMR on T2-weighted images between the left and right lobes.

**Figure 5 Relationships between MRI variables and hepatic injury score based on the scoring criteria.** The ADC value and LMR decreased as the hepatic injury score increased, and the correlations are statistically significant for each. ADC: Apparent diffusion coefficient; LMR: Liver-to-muscle ratio; MRI: Magnetic resonance imaging.