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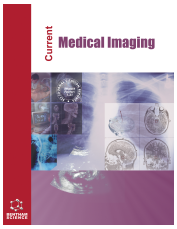

RESEARCH ARTICLE

4D Flow MRI of Portal Vein Hemodynamics in Healthy Volunteers and Patients with Chronic Liver Disease

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Abstract:

Aim:

To identify age-matched healthy volunteers, non-cirrhotic chronic liver disease (CLD) and cirrhotic patients based on portal hemodynamic parameters using 4D flow MRI.

Methods:

A total of 10 age-matched healthy volunteers and 69 CLD patients were enrolled and underwent 4D flow MRI prospectively. 4D flow MR images were processed by an MD in biomedical engineering working on the GTFlow platform. Portal hemodynamic parameters include net flow (mL/cycle), flow volume per second through the lumen (mL/sec), average flow velocity (cm/sec), and maximum flow velocity (cm/sec). The difference in portal hemodynamic parameters of 4D flow MRI was compared among healthy volunteers, non-cirrhotic CLD patients and patients with cirrhosis by one-way ANOVA or Kruskal-Wallis nonparametric test and post hoc tests.

Results:

10 CLD patients without cirrhosis and 56 patients with cirrhosis were eventually included, along with 10 healthy volunteers who were divided into three groups. 3 patients with cirrhosis whose image quality did not meet the requirements were excluded. There were no significant differences in portal hemodynamic parameters among the three groups except portal average velocity ($P > 0.05$). There was no statistical difference in all portal hemodynamic parameters of 4D flow MRI between healthy volunteers and patients with cirrhosis ($P > 0.05$). There were significant differences in portal average velocity between non-cirrhotic CLD patients, healthy volunteers and patients with cirrhosis, respectively (11.44±3.93 *vs* 8.10±2.66, P=0.013; 11.44±3.93 *vs* 8.60±2.22, P=0.007).

Conclusion:

Portal average velocity obtained by 4D flow MRI can be an auxiliary means to identify cirrhosis in patients with CLD.

Keywords: Chronic liver disease, Cirrhosis, Portal vein, 4D flow MRI, Hemodynamics, Patients.

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1. INTRODUCTION

Cirrhosis is the end-stage of chronic liver disease (CLD) caused by various causes, and it is a disease that needs great attention in the world. Portal hypertension is the most important event in the course of cirrhosis. It is a clinical syndrome caused by the continuous increase of portal vein pressure. Accompanied by the increase of portal vein pressure, the portosystemic collateral circulation will format, and about 50% of patients with portal hypertension may develop esophagogastric varices [1, 2]. When the severity of liver

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disease reaches a certain degree, most of the decompensated events of liver cirrhosis will occur, such as gastroesophageal variceal rupture and bleeding, ascites, hepatic encephalopathy, *etc*., which will increase the risk of death.

Moreover, due to liver fibrosis, portal flow resistance increases gradually, leading to compensatory increases in cardiac output. Thus, portal flow volume elevates, resulting in increased portal vein pressure [3, 4]. Therefore, a comprehensive, non-invasive understanding of liver hemodynamics has great guiding significance for the clinical diagnosis and treatment of patients with chronic liver disease.

In the past decades, especially in the last decade, with the progress of MRI techniques, a time-resolved 3D phase-contrast MRI technique based on velocity encoding (VENC) with three directions, namely 4D flow MRI, has made great progress in clinical research. Especially, the application of 4D flow MRI in the cardiothoracic vessels has been gradually carried out in clinical practice [5 - 8]. However, up to now, the application in abdominal vessels, especially liver vessels, is relatively rare, mainly focusing on the technical level and consistency of research. For example, the 2021 review by Haarbye SO *et al.* [9] found that compared with Doppler ultrasound blood flow imaging, 4D flow MRI has higher inter-observer consistency (good or extremely good), showing unique advantages in displaying complex and varied abdominal vascular structure, and can simultaneously provide hemodynamic parameters of multiple vessels which is obviously better than ultrasonic blood flow imaging. In addition, for the study of clinical practice, most research objects are healthy subjects and patients with cirrhosis or portal hypertension while ignoring the group of patients with CLD who have not progressed to cirrhosis. Therefore, to fill the void in such a line of research, the aim of this study was to compare portal hemodynamic parameters in healthy volunteers, non-cirrhotic patients with CLD and cirrhotic patients using 4D flow MRI.

2. METHODS

2.1. Subjects

This prospective study was approved by the hospital ethics committee and followed the guidelines of Helsinki Declarations, and all subjects signed written informed consent. From October 2021 to May 2022, 69 patients with CLD with or without cirrhosis admitted to our hospital were enrolled. Another 10 age-matched healthy volunteers with no history of liver disease were recruited for this study. A 4D flow MRI scan was performed on all enrolled subjects. All subjects are required to be over 18 years old. The diagnosis of CLD and cirrhosis is based on pathological diagnosis, clinical history, ultrasound elastography, gastroduodenal endoscopy, imaging examination, *etc* [10]. All subjects were asked to fast for at least 4-6 hours prior to 4D flow MRI.

Exclusion criteria: (1) previous history of surgical resection of liver lesions, transjugular intrahepatic portosystemic stent shunt (TIPS), liver or spleen intervention, *etc*.; (2) There are contraindications to MRI examination (metal implants, claustrophobia, *etc*.); (3) Patients cannot cooperate to complete MRI examination, or images cannot meet the diagnostic requirements.

2.2. 4D Flow MR Image Acquisition

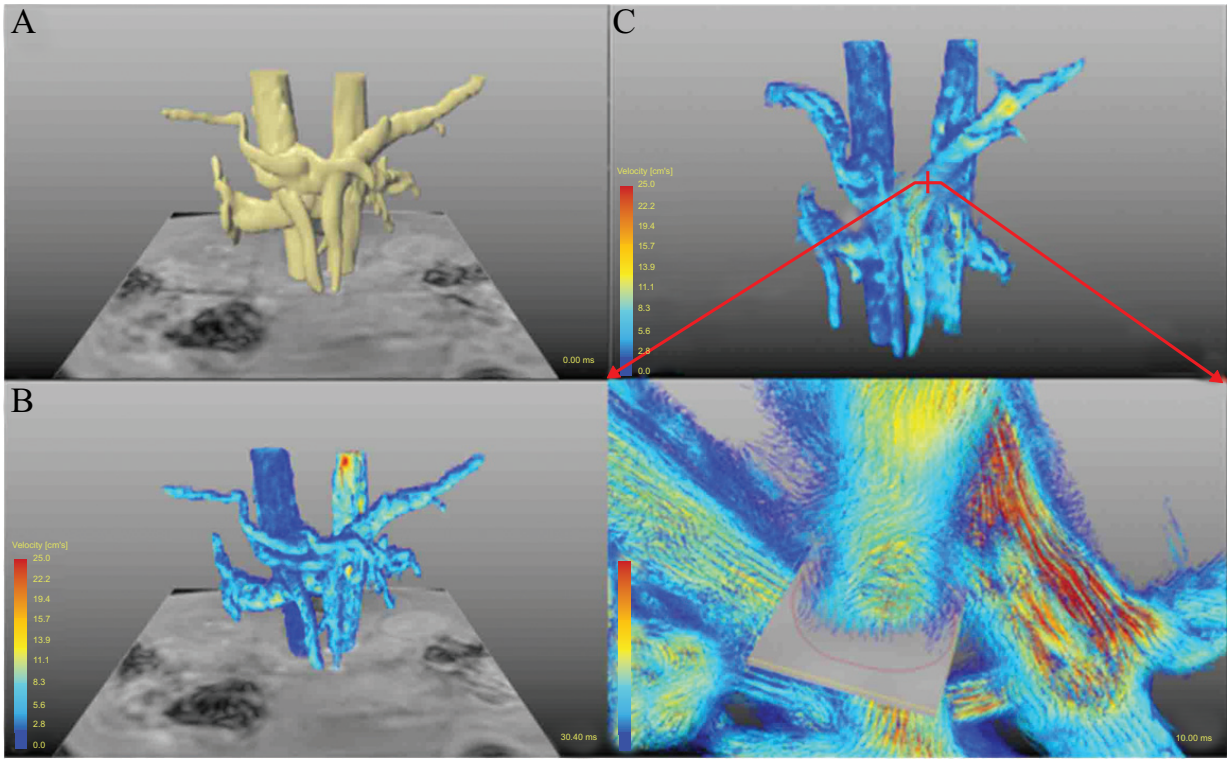
Our studies were performed on a 3T scanner (Philips Ingenia, Philips Healthcare, The Netherlands) with a 32-channel phased-array body coil. We applied a time resolution and three-dimensional phase contrast gradient echo pulse sequence with the SENSE technique and three-directionally different VENC in the state of free breathing. All subjects were scanned after 4-6 hours of fasting. An adaptive respiratory gating with a 7% acceptance window was placed in the junction of the liver and lung in order to reduce image artifacts, and an electrocardiogram gating was accomplished with a peripheral pulse. Signals were acquired during each cardiac cycle (RR interval), and the scanning time is nearly 10 minutes. According to different breathing patterns, the scanning time slightly changes. MRI parameters included: echo time (TE) = 2.3msec, repeat time (TR) = 3.3msec, scan layers = 25 layers, layer spacing = 0 mm, imaging volume = 200×175×75 $mm^{3,}$ acquisition matrix = 2.94×3.24×3.00 mm^3, reconstruction matrix = 0.78×0.78×3.00 mm^3, flip Angle = 7°, number of echo chains = 4, Water fat displacement/acquisition bandwidth = 0.113pix/3828.5Hz. Using the SENSE technique, the acceleration factor of the front and rear directions was 1.5, the front and rear directions were set as the phase encoding direction, and the VENC of the three directions (foot and head, right and left, and anterior and posterior) were 75/50/150 cm/sec respectively. The time-averaged magnitude and velocity images of the three velocity vector fields were obtained through offline reconstruction.

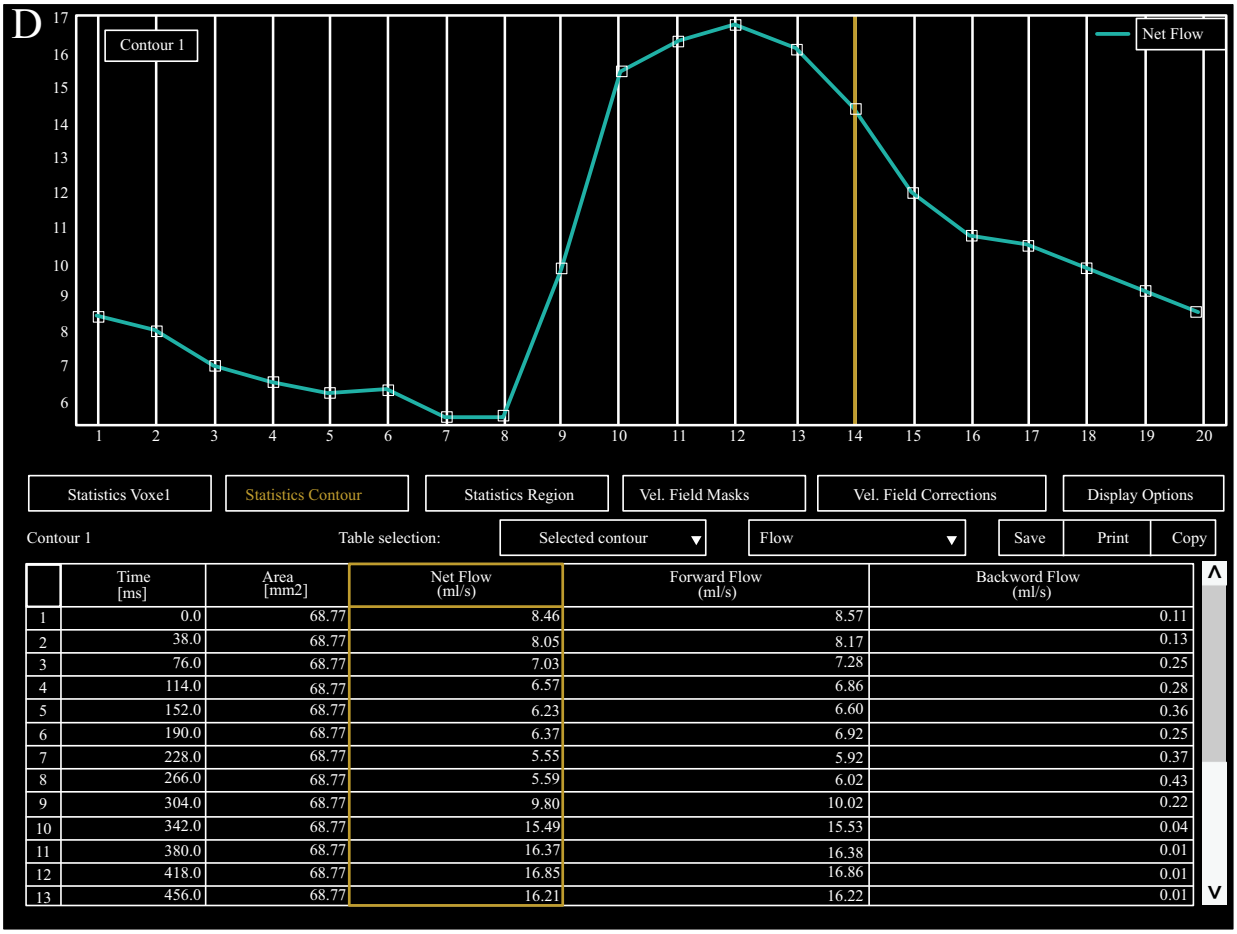
2.3. Image Processing

4D flow MR images were processed by an MD in biomedical engineering working on the GTFlow software platform (version 2.2.15, GyroTools, Zurich, Switzerland). The operator is unaware of the subjects' clinical information. Before any image processing, eddy current correction is first carried out [11], and then appropriate velocity antialiasing is carried out on the images to obtain enough effective information. Based on the above images, segmentation was processed to generate images of the 3D visualization and display vascular contours clearly. Place the cut plane perpendicular to the main portal vein long axis proximal to the hepatic hilum for quantitative observation of hemodynamic parameters which was adjusted according to the captured complete cardiac cycle and heart rate. The parameters mainly include the flow volume through the vascular lumen in one cardiac cycle, that is, the net flow (mL/cycle), the flow volume through the vascular lumen per second (mL/sec), the average velocity (cm/sec) and the maximum or peak velocity (cm/sec). Portal hemodynamic parameters measured on 4D flow MRI are shown in Fig. (**1**).

2.4. Statistical Analysis

All subjects were divided into three groups: age-matched health volunteers, non-cirrhotic CLD patients, and patients with cirrhosis. Continuous variables with normal distribution were represented by mean ± standard deviation, otherwise, by median (IQR), and categorical variables are represented by number (percentages). One-way ANOVA was used for inter-





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	Time [ms]	Area [mm2]	Net Flow (ml/s)	Forward Flow (ml/s)	Backword Flow (ml/s)
1	0.0	68.77	8.46	8.57	0.11
2	38.0	68.77	8.05	8.17	0.13
3	76.0	68.77	7.03	7.28	0.25
4	114.0	68.77	6.57	6.86	0.28
5	152.0	68.77	6.23	6.60	0.36
6	190.0	68.77	6.37	6.92	0.25
7	228.0	68.77	5.55	5.92	0.37
8	266.0	68.77	5.59	6.02	0.43
9	304.0	68.77	9.80	10.02	0.22
10	342.0	68.77	15.49	15.53	0.04
11	380.0	68.77	16.37	16.38	0.01
12	418.0	68.77	16.85	16.86	0.01
13	456.0	68.77	16.21	16.22	0.01

Fig. (1). Measurement of visualized hemodynamic parameters in 4D flow MRI. (**A**). Visual images after vascular segmentation; (**B**). Streamline observation based on visual vascular images; (**C**). Selection of vessel cross section; (**D**). 4D flow MRI measurement of hemodynamic parameters.

group comparison of continuous variables with normal distribution and homogeneity of variance, and post hoc tests were performed for statistical differences. Kruskal-Wallis H test and post hoc tests were used for inter-group comparison of continuous variables without normal distribution. The Kruskal-Wallis rank sum test was used for the comparison of categorical variables. Analysis was performed by using SPSS 26.0 (Inc. Chicago, IL, USA) and GraphPad Prism v8.0.2 (GraphPad Software, La Jolla, CA). $P < 0.05$ means the difference is statistically significant.

3. RESULTS

A total of 76 healthy volunteers and CLD patients were enrolled, including 10 healthy volunteers, 10 CLD patients without cirrhosis, and 56 patients with cirrhosis. 3 patients with cirrhosis whose image quality did not meet the requirements were excluded. The mean age was 50.96 ± 9.61years. There were 50 males, accounting for 65.8% of the total population. The mean BMI was 23.82 ± 3.13. There was no significant statistical difference between the above indexes. Hepatitis B virus infection was the main cause of CLD in 40 patients, accounting for 52.6% of the total CLD patients (Table **1**). There were no significant differences in the other three hemodynamic parameters except the portal venous average velocity (cm/s). The average velocity, maximum velocity, net flow and flow volume of the portal vein were 8.90 ± 2.69 cm/sec, 22.48 (19.34-26.50) cm/sec, 12.15 ± 3.87 mL/cycle, 15.77 ± 5.40 mL/sec, respectively. Basic information of patients and healthy volunteers included in the study and portal hemodynamic parameters of 4D flow MRI are shown in Table **2**.

Table 1. Demographics of healthy volunteers and patients with CLD.

-	All (n=76)	Health Volunteers (n=10)	Non-cirrhotic CLD Patients (n=10)	Cirrhotic Patients (n=56)	P Value
Age	50.96 ± 9.61	47.30 ± 6.67	50.50 ± 8.57	51.66 ± 10.15	0.438
Sex	-	-	-	-	0.528
Male	50 (65.8%)	7 (70%)	5 (50%)	38 (67.9%)	-
Female	26 (32.4%)	3 (30%)	5 (50%)	18 (32.1%)	-
BMI	23.82 ± 3.13	23.76 ± 1.78	23.95 ± 3.83	23.81 ± 3.23	0.99
Etiology of liver disease	-	-	-	-	<0.001*
Without liver disease	10 (13.2%)	10 (100%)	-	-	-
Hepatitis B virus	40 (52.6%)	-	7 (70%)	33 (58.9%)	-
Hepatitis C virus	5 (6.6%)	-	-	5 (8.9%)	-
Alcohol	7 (9.2%)	-	-	7 (12.5%)	-
Drug-induced	5 (6.6%)	-	3 (30%)	2 (3.6%)	-
Other	9 (11.8%)	-	-	9 (16.1%)	-
Child-Pugh stage	-	-	-	-	0.691
Grade A	-	-	7 (70%)	28 (50%)	-
Grade B	-	-	3 (30%)	25 (44.6%)	-
Grade C	-	-	0	3 (5.4%)	-
Child-Pugh score	-	-	5.5 (5-7)	6.5 (6-7)	0.056
MELD score	-	-	7.99 (7.18-11.46)	8.94 (7.97-10.98)	0.617

Note: Continuous variables with normal distribution were expressed as mean ± standard deviation, and one way ANOVA was performed for statistical analysis. While categorical variables were expressed as number (percentages), and Kruskal-Wallis rank sum test was used for comparison. P value is the comparison among the three groups, and * indicates P value < 0.05 which represents statistically significant difference.
BMI:body mass index; MELD: model for end-stage liver disease.

Table 2. Portal venous hemodynamic parameters in healthy volunteers and patients with CLD.

-	All (n=76)	Health Volunteers (n=10)	Non-cirrhotic CLD Patients (n=10)	Cirrhotic Patients (n=56)	P Value
Average velocity (cm/sec)	8.90 ± 2.69	8.10 ± 2.66	11.44 ± 3.93	8.60 ± 2.22	0.004*
Maximum velocity (cm/sec)	22.48 (19.34-26.50)	25.34 (21.73-29.01)	25.57 (19.68-31.60)	21.94 (18.99-26.22)	0.095
Net flow volume (mL/cycle)	12.15 ± 3.87	11.80 ± 3.35	11.71 ± 3.35	12.28 ± 4.05	0.871
Flow volume (mL/sec)	15.57 ± 5.40	13.61 ± 4.16	16.45 ± 6.34	15.75 ± 5.43	0.443

Note: Continuous variables with normal distribution were expressed as mean ± standard deviation, and one way ANOVA was used for inter-group comparison. Continuous variables without normal distribution were expressed as the median (Q1-Q3), and Kruskal-Wallis H test was used for inter-group comparison. P value is the comparison among the three groups, and * indicates P value < 0.05 which represents statistically significant difference.

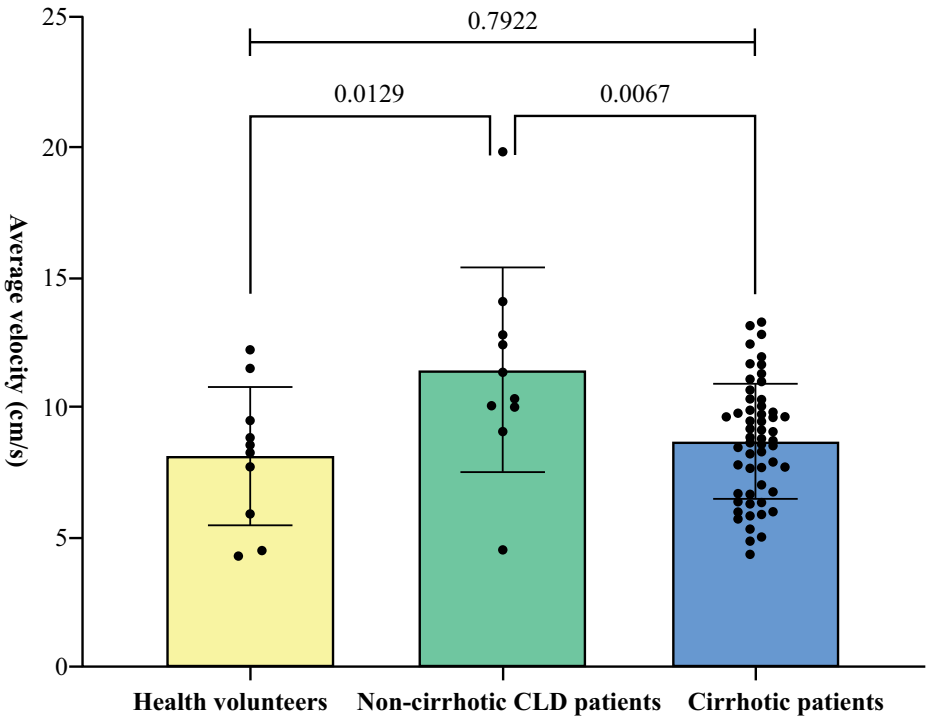

Fig. (2). Post hoc tests of portal venous average velocity among three groups.

4D flow MRI portal venous average velocity, maximum velocity, net flow volume per cardiac cycle, and flow volume per second were measured in healthy volunteers and patients with CLD. By comparing the three groups, we found that the portal venous average velocity was different among the three groups (P = 0.004), and there was no significant statistical difference in the other three hemodynamic parameters (P = 0.095, 0.871 and 0.443, respectively). Post hoc tests of average velocity showed that there was a statistical difference between the non-cirrhotic CLD group and the other two groups. The average velocity in the non-cirrhotic CLD group (11.44 ± 3.93cm/s) was higher than that in the other two groups (8.10 ± 2.66 cm/s and 8.60 ± 2.22cm/s, respectively), and the P value was 0.013 compared with healthy volunteers and 0.007 compared with patients with cirrhosis. There was no significant difference between healthy volunteers and patients with cirrhosis (P = 0.792). The comparison of the portal venous average velocity of the three groups is shown in Fig. (**2**).

4. DISCUSSION

This study included three groups of age-matched healthy volunteers, non-cirrhotic patients with CLD and cirrhotic patients. It analyzed the changes of portal venous hemodynamic parameters measured by 4D flow MRI in the three groups. In order to avoid the influence of age, sex, height and weight on portal venous hemodynamic parameters, the values of age, sex and BMI among the three groups included were similar to each other, and there was no statistical difference. Since there is a healthy control group, there must be differences in etiology among the three groups, which is relevant to the purpose of this study. In our study, 4D flow MRI was used to measure the average velocity, maximum velocity, net flow and flow volume of portal veins in the three groups. Firstly, it was found that the average velocity of portal veins was statistically different among the three groups, while other hemodynamic parameters were not statistically different among the three groups. Secondly, Post hoc tests of the average velocity of the three groups showed that the average velocity of the non-cirrhotic patients with CLD was statistically different from that of healthy volunteers and cirrhotic patients, and there was no difference between the latter two groups.

Previous reports [12 - 15] showed that there was no statistical difference in hemodynamic parameters between healthy volunteers and patients with cirrhosis, which was consistent with our study. Moreover, the portal hemodynamic parameters measured by Stankovic Z *et al.* [13] in healthy volunteers were similar to our measurement results. However, few studies have been reported on non-cirrhotic patients with CLD. Bane O *et al.* [16] conducted a 4D flow MRI study on the abdomen of 27 patients with CLD without cirrhosis and 25 patients with liver cirrhosis under one breath holding and showed that the peak, average, and net flow rates of portal veins were not statistically different between non-cirrhotic and cirrhotic patients. However, the authors found that the splenic vein cross-sectional area and mean flow rate of the right hepatic vein could distinguish between cirrhotic and non-cirrhotic patients, and their values increased and were statistically different in cirrhotic patients. This study is not entirely consistent with our study, which showed significant differences in portal venous average velocity between the two. The reason for this may be different from the scanning methods used in the two studies. The study by Bane O *et al.* [16] is a rapid scanning technique under one breath holding, which takes only 22 seconds to collect images of 24 cardiac cycles, while our scan takes about 10 minutes to collect images under free breathing. Respiratory status and scanning time may have

a certain influence on the results, and the former study focuses on the feasibility analysis of scanning technology without giving the specific measurement value of each vessel, which makes it impossible for us to compare and analyze the problems objectively. Thirdly, it may be related to the sample deviation of patients collected. Although there are many patients with cirrhosis in our study, there are few non-cirrhotic patients with CLD, and there is no matching number of patients with cirrhosis, which may lead to selection bias of the results. Therefore, it is necessary for us to increase the sample size for a more adequate study and analysis in the future. If the same results are still obtained, a new method for non-invasive diagnosis of cirrhosis in patients with CLD will be added. In addition, the study by Brunsing *et al.* [15] provides a more clinically interesting perspective. Though the authors also found that there is no difference in portal venous flow volume between patients without CLD and patients with cirrhosis, according to whether the portosystemic shunt in patients with cirrhosis, the author grouped again. The study found that there were significant differences in portal venous flow volume among patients with portosystemic shunt, patients without CLD and patients with cirrhosis without portosystemic shunt, respectively. The emergence of portosystemic shunt, in particular, is often indicative of advanced cirrhosis with significant portal hypertension, which may exhibit different portal hemodynamic characteristics from those of healthy volunteers and non-cirrhotic patients with CLD. Combined with the fact that most patients with liver cirrhosis in this study had progressed to end-stage liver disease, and the proportion of patients with varicose veins and portosystemic shunt was relatively high, we speculated that portal venous hemodynamics would be affected before and after the formation of portosystemic shunt. In patients with CLD that have not progressed to liver cirrhosis, portal venous hemodynamics compared with healthy volunteers may have some changes. But when progressing to the formation of a portosystemic shunt, the portal venous blood bypass to the systemic circulation in part, which reduces the pressure of the portal vein, and may influence some parameters of portal venous hemodynamics. This viewpoint needs further verification and analysis.

4D flow MRI can be utilized to observe hemodynamic changes in the portal vein system in liver diseases for a few years. Some researchers have proposed more intriguing concepts [17, 18]. For instance, they compare the difference in portal blood flow between eating and postprandial states and analyze the reserve capacity of portal blood flow to differentiate the severity of liver disease. Although this idea is innovative, we believe that this method is relatively complex to perform and requires specific examination time points, making it challenging to implement in clinical practice. Therefore, further research and optimization are necessary at present.

There are some limitations in this study. First, due to the small number of age-matched healthy volunteers and non-cirrhotic CLD patients in this study, it is necessary to increase the sample size for verification and analysis to avoid sample bias caused by individual differences and other reasons. Secondly, although the feasibility, consistency and repeatability of 4D flow MRI have been extensively verified and analyzed in many previous literatures, it is not studied in this research. In addition, there is a lack of corresponding verification analysis for the results of this study in different vendors and devices with different magnetic field strengths, which requires further research by more medical centers. Thirdly, the segmentation method of the image is likely to have some influence on the results. In this study, the manual segmentation method is adopted to process the image, which inevitably produces errors. Since the vast majority of previous articles have adopted manual image segmentation methods and, the results are basically consistent with the results of this study. However, to the best of our knowledge, a number of automatic segmentation techniques have emerged [19 - 21], there are no uniform standards yet, and there is no research on side-by-side comparisons of multiple segmentation methods. Therefore, we believe that after this study, many researchers interested in this field will devote themselves to research. Finally, other parameters of subjects were not included in this study, which may have some influence on the results and can be analyzed in future studies.

CONCLUSION

4D flow MRI is a scanning technique with very promising development prospects, especially in cervical vessels and the cardiovascular system. At present, 4D flow MRI has been gradually applied to abdominal vessels with complex blood flow distribution. So far, 4D flow MRI studies on liver hemodynamics have mainly focused on cirrhosis, particularly in the end-stage of portal hypertension [22]. Through our preliminary study on age-matched healthy volunteers and patients with CLD, it was found that there was no significant difference in hemodynamic parameters between healthy volunteers and patients with cirrhosis, and it was not possible to distinguish healthy people from patients with cirrhosis by 4D flow MRI hemodynamic parameters. For patients with CLD, portal venous average velocity measured by 4D flow MRI has a significant statistical difference between patients with and without cirrhosis, which may be helpful for the diagnosis of patients with cirrhosis.

ABBREVIATIONS

CLD = Chronic Liver Disease

TIPS = Transjugular Intrahepatic Portosystemic Stent

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval was received for this study from the Chinese PLA General Hospital Institutional Review Board (Decision date Sept 24, 2021. Decision number KY-2021-9-17-1).

HUMAN AND ANIMAL RIGHTS

No animal were used that are the basis of this study. This prospective study was approved by the hospital ethics committee and followed the guidelines of Helsinki Declarations.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants of this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information is available within the article.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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