学位論文（博士）

Lobar hepatic steatosis: Association with portal flow hemodynamics evaluated by multiphasic dynamic contrast-enhanced CT
（区域性脂肪肝：ダイナミック造影 CT における門脈血行動態との関連）

氏名　河野　洋佑
所属　山口大学大学院医学系研究科
医学専攻　放射線医学講座

令和 6 年 11 月

学位論文の関連論文の研究背景及び要旨

所属　放射線医学講座
氏名　河野　洋佑

〔題名〕
Lobar hepatic steatosis: Association with portal flow hemodynamics evaluated by multiphasic dynamic contrast-enhanced CT
（区域性脂肪肝：ダイナミック造影 CT における門脈血行動態との関連）

European Journal of Radiology　DOI: 10.1016/j.ejrad.2023.110688.　（2023 年 3 月掲載）

研究背景と目的

脂肪肝の原因にはいくつかあるが、近年非アルコール性脂肪性肝疾患の有病率が著しく増加している。脂肪肝の終末像として線維化、肝硬変、肝細胞癌の経過を辿ることから、脂肪肝の早期診断や重症度の適切な評価、病因解明が臨床的に重要である。脂肪肝の病型としてびまん性脂肪肝が一般的ではあるが、日常的に区域性脂肪肝の症例をしばしば経験することがある。これは脂肪を生成する消化性因子が豊富に含まれている上腸間膜静脈(superior mesenteric vein:SMV)の灌流の影響として説明可能かもしれないが、この仮説を支持する決定的な科学的証拠はほとんど存在しない。そこで Dynamic CT における動脈相の脾静脈(splenic vein:SV)と SMV の造影効果の違いに着目した。SV は造影剤の早期静脈還流のため、通常造影効果が見られるが、SMV では腸間膜循環が長い影響で通常造影効果が見られない。従って、動脈相 CT における肝実質の門脈灌流の造影効果の主体は脾静脈と思われ、区域性脂肪肝症例の動脈相 CT において脂肪沈着部の造影効果が非脂肪沈着部位と比較して有意に減少していれば、上記仮説を支持するのではないかと考えた。そこで、本研究は Dynamic CT を用いて門脈血行動態と区域性脂肪肝の関連を評価することを目的とした。

対象と方法

当院の放射線科データベースの 2015 年 7 月から 2020 年 6 月の間に Dynamic CT を撮像された患者の内、脂肪肝が疑われた 423 名を検出した。この中から腹部手術の既往、3cm を超える肝腫瘤、門脈血栓、Dynamic 撮像不良、動脈相 CT で既に SMV に造影剤の灌流が十分ある症例を除いた 235 名を研究対象とした。先行研究に倣って、本研究では肝実質の CT 値<48(HU)を脂肪肝、右葉と左葉の CT 値の差が 10 を超えるものを区域性脂肪肝、超えないものをびまん性脂肪肝と定義した。区域性脂肪肝は 77 名、内訳として右葉の区域性脂肪肝が 67 名、左葉の区域性脂肪肝が 10 名であった。びまん性脂肪肝は 158 名、内訳として非脂肪沈着領域(focal spared area:FSA)ありが 76 名、FSA なしが 82 名であった。それぞれの症例で肝右葉と左葉に ROI(100mm^2 以上)を設定し、CT 値(HU)を単純および動脈相 CT で測定した(図 1.2)。造影増強(contrast enhancement:CE)値は、単純と動脈相の CT 値の差として算出した。びまん性脂肪肝症例の内、 FSA があるものは可能な範囲で ROI を設定し、脂肪沈着領域と

FSA で同様に測定した(図 3)。

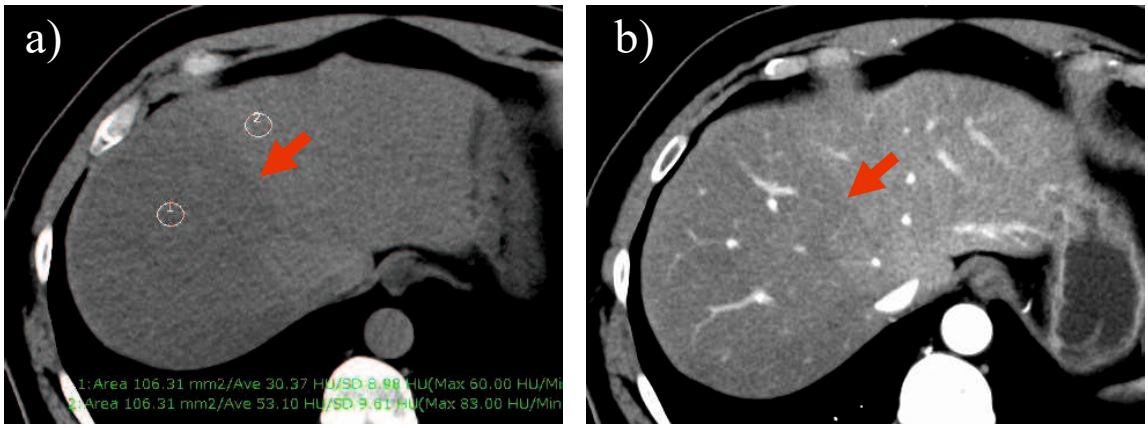

図 1　右葉の区域性脂肪肝　(a)単純 CT　(b)動脈相 CT

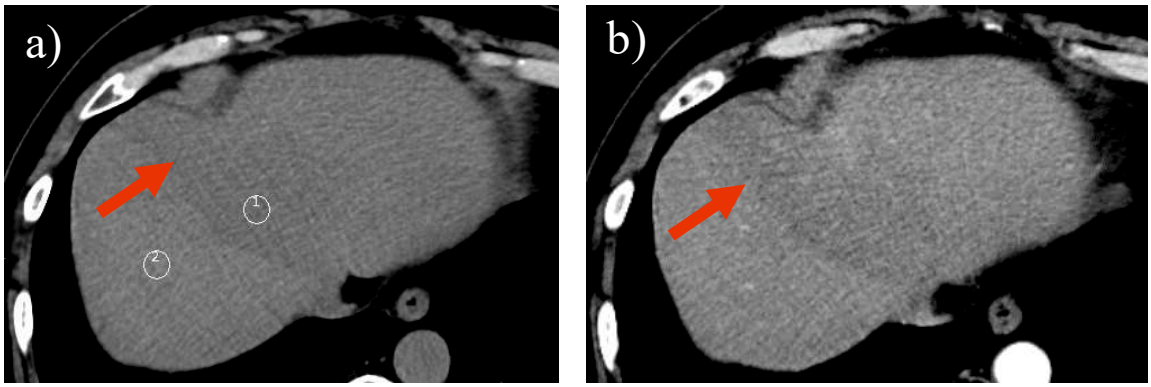

図 2　左葉の区域性脂肪肝　(a)単純 CT　(b)動脈相 CT

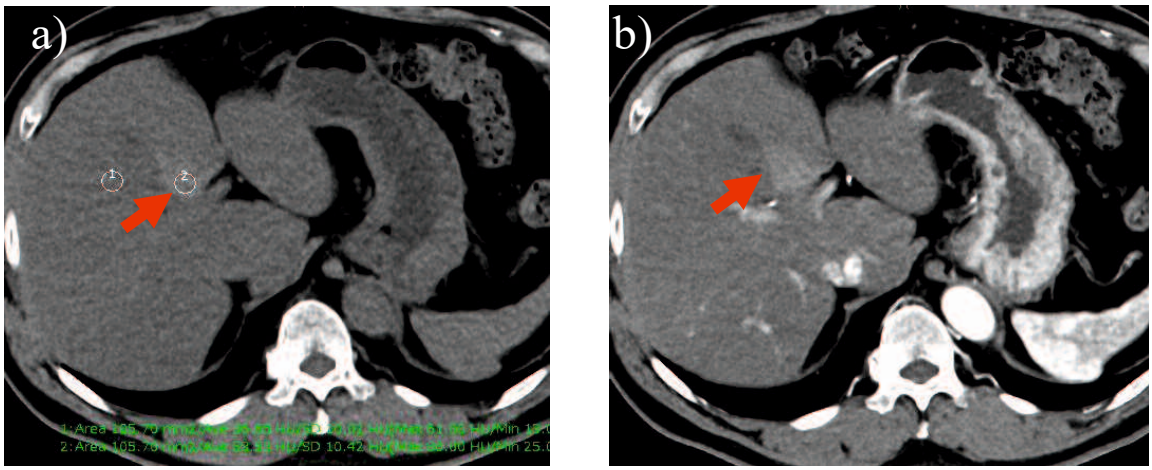

図 3　びまん性脂肪肝、FSA あり　　(a)単純 CT　(b)動脈相 CT

また、区域性脂肪肝において SV-SMV 角 (spleno-mesenteric confluence:SMC)を再構成冠状断像で測定した。統計解析には Shapiro-Wilk 検定、Wilcoxon の符号順位検定、2 標本 t 検定を用いた。

結果

区域性脂肪肝とびまん性脂肪肝の右葉と左葉の CE 値の比較を表 1 に示す。

Type of steatosis	Median contrast enhancement values (HU)		
	Right hepatic lobe	Left hepatic lobe	*P*-value
Right lobar steatosis group (n=67)	13 [7-19]	23 [13-33]	<0.01
Left lobar steatosis group (n=10)	16 [14.5-22]	15.5 [11.75-21.5]	0.20
Diffuse steatosis group (n=82)	10.5 [4-20]	11.5 [7-20.3]	<0.01

Data represent the median values with the 25th and 75th percentiles

表 1 区域性脂肪肝とびまん性脂肪肝の CE 値の比較

まず、区域性脂肪肝は右葉に多い傾向であった(87%)。右葉の区域性脂肪肝では CE 値は右葉が左葉より有意に低かった(P<0.01)。びまん性脂肪肝でも CE 値は右葉が左葉より有意に低く(P<0.01)、単純 CT での CT 値は右葉で有意に低かった(38.5 [30.75–42] vs 38.5 [33–44.25] HU, P < 0.01)。一方、左葉の区域性脂肪肝では CE 値は左葉が右葉よりも低かったが、有意差は認められなかった(P=0.20)。びまん性脂肪肝では 48 名が胆嚢窩に、28 名が内側区域に FSA が認められ、それぞれ脂肪沈着部位は FSA と比較して CE 値に有意（15.5[9-24.3]HU vs 17[8.3-32.5]HU、P = 0.01、11 [6-25.5] HU vs 23 [10.3-43.8], P < 0.01）に低かった。区域性脂肪肝における平均 SMC は左葉の区域性脂肪肝(96.2±11.9)が右葉の区域性脂肪肝(104.8±16.4)より小さい傾向にあったが、有意差は認められなかった(P=0.098)。

考察

本研究では区域性脂肪肝は右葉に多い傾向であり、右葉の区域性脂肪肝では CE 値は右葉が左葉より有意に低く、これらの結果から SMV の灌流は右葉優位に分布していることが示唆された。SMV からの血流には豊富な脂肪を生成する消化性因子が含まれており、肝細胞に脂肪性変化をもたらす可能性がある。

SMV や SV の血流分布に関しては依然議論の余地はあるが、血管造影とシンチグラフィーの所見に基づくいくつかの研究では、SV は肝左葉優位に、SMV は肝右葉優位に灌流するという選択的門脈血層流の存在が支持されている。これにより肝臓は右葉と左葉で門脈灌流のパターンが異なり、区域性脂肪肝が生じている可能性がある。一方、本研究では区域性脂肪肝の 13%は左葉の区域性脂肪肝であり、CE 値は左葉が右葉より低い傾向であった。これは SV が肝右葉優位に、SMV が肝左葉優位に灌流することを示唆している。MR portography を用いた以前の研究では 10%程で SV の流れは門脈の右側に分布しており、SV の流れが肝右葉優位であることを示す本研究結果の頻度と同様であった。Barnett らによるモデルを用いた実験的研究では SV は灌流が増加すると、門脈右側を上行し肝右葉に優先的に分布することが示唆された。さらに別の研究では門脈渦状流が血流分布に及ぼす影響を検討しており、門脈渦状流形成の程度は SV と SMV の合流角度(SMC)や方向と有意な相関があることが示された。例えば、SMC

の角度が小さくなると、SV から門脈左枝への灌流は減少し、SMV から門脈左枝へ灌流が増加する傾向にあった。本研究では、左葉の区域性脂肪肝で SMC が小さい傾向にあり、有意差は認めなかったが、先行研究を支持するものであった。ただ、先行研究では門脈渦状流の程度は SMC の形状や 3 次元的配向とも相関しており、他にも肝硬変患者でより強い相関を示すことや食事の影響も関与していることなどが示されており、門脈流の動態と分布にはいくつかの要因が関与していることには注意すべきである。

本研究ではびまん性脂肪肝で CE 値が区域性脂肪肝より総じて低く、CE 値は右葉が左葉より有意に低かった。これはびまん性脂肪肝では肝両葉が SMV 灌流の影響を強く受けているが、肝右葉で生理的な SMV 層流の影響が強いことを示唆していると考えられる。

結語

区域性脂肪肝などの脂肪沈着の病態は、門脈血行動態の局所的変化と関連している(SMV の灌流が優位な部位に脂肪沈着が生じている)可能性がある。

European Journal of Radiology 160 (2023) 110688

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Lobar hepatic steatosis: Association with portal flow hemodynamics evaluated by multiphasic dynamic contrast-enhanced CT

Yosuke Kawano, Masahiro Tanabe *, Fumi Kameda, Mayumi Higashi, Kenichiro Ihara, Masaya Tanabe, Atsuo Inoue, Taiga Kobayashi, Takaaki Ueda, Katsuyoshi Ito

Department of Radiology, Yamaguchi University Graduate School of Medicine, 1-1-1, Minami-Kogushi, Ube, Yamaguchi 755-8505, JAPAN

ARTICLE INFO

Keywords:
Lobar hepatic steatosis
Dynamic contrast-enhanced CT
Splenic vein
Superior mesenteric vein
Portal flow hemodynamics

ABSTRACT

Purpose: This study aimed to evaluate the association of portal flow hemodynamics with lobar hepatic steatosis by means of dynamic contrast-enhanced (DCE) CT.

Methods: The study population consisted of 235 patients, 77 with lobar hepatic steatosis (right, n = 67; left, n = 10), 158 with diffuse hepatic steatosis with (n = 76) and without (n = 82) a focal fatty spared area. CT attenuation values (Hounsfield units: HU) of the liver with and without hepatic steatosis were measured in unenhanced and arterial-phase CT. The contrast enhancement (CE) values were calculated as the difference in HU values between unenhanced and arterial-phase CT.

Results: In 67 patients with lobar steatosis of the right lobe, the median CE values of the areas of right lobar steatosis were significantly lower than those of the non-fatty left lobe (13 [IQR 7–19] vs 23 [13–33] HU, $P < 0.01$), suggesting dominant SMV flow to the right lobe with lobar hepatic steatosis. Conversely, in 10 patients with lobar steatosis of the left lobe, the median CE values of the areas of left lobar steatosis were lower than those of the non-fatty right lobe (15.5 [11.75–21.5] vs 16 [14.5–22] HU); however, this difference was not statistically significant ($P = 0.20$). In 76 patients with a focal fatty spared area, there were significant differences in the median CE values between hepatic steatosis areas and focal fatty spared areas in the gallbladder fossa group ($P = 0.01$) and in the segment IV group ($P < 0.01$).

Conclusion: Lobar hepatic steatosis may be associated with regional changes of the portal flow hemodynamics (i.e., predominant perfusion from the SMV flow to the lobes with steatosis).

1. Introduction

Hepatic steatosis is frequently and incidentally detected on unenhanced CT as the areas of decreased attenuation. Although there are several causes of hepatic steatosis, the prevalence of non-alcoholic fatty liver disease (NAFLD) has increased significantly in recent years [1]. NAFLD is associated with the risk of developing non-alcoholic steatohepatitis (NASH), leading to fibrosis, cirrhosis, and finally to the development of hepatocellular carcinoma (HCC) [2]. Therefore, an early diagnosis, the proper assessment of the severity of steatosis, and the elucidation of the pathogenesis of this disease are clinically important.

Diffuse hepatic steatosis that is homogeneously involved by fat accumulation is the most prevalent form of fatty liver disease [3]. However, hepatic steatosis may present with different patterns of distribution and sparing. For instance, we have often encountered patients with lobar hepatic steatosis with expected anatomical border mostly between the left and right lobes of the liver on unenhanced CT. This finding may be explained by the hypothesis that the superior mesenteric vein (SMV) flow, which contains lipogenic alimentary factors (e.g., a high concentration of fructose and short- or medium-chain fatty acids), is preferentially distributed to the hepatic lobe with fatty infiltration [3,4]. However, there is little conclusive scientific evidence to support

Abbreviations: DCE, dynamic contrast-enhanced; HU, Hounsfield unit; NAFLD, non-alcoholic fatty liver disease; ROI, region of interest; SV, splenic vein; SMC, spleno-mesenteric confluence; SMV, superior mesenteric vein.

Peer review under responsibility of If file "editor conflict of interest statement" is present in S0, please extract the information and add it as a footnote (star) to the relevant author. The sentence should read (and be amended accordingly): Given his/her role as EditorinChief/Associate Editor/Section Editor <NAME of Editor> had no involvement in the peerreview of this article and has no access to information regarding its peerreview..

* Corresponding author.
E-mail address: m-tanabe@yamaguchi-u.ac.jp (M. Tanabe).

https://doi.org/10.1016/j.ejrad.2023.110688
Received 29 September 2022; Received in revised form 27 December 2022; Accepted 3 January 2023
Available online 5 January 2023

this hypothesis.

On arterial-phase multiphasic dynamic contrast-enhanced (DCE) CT images, the splenic vein (SV) usually shows high attenuation because of early venous return with contrast agent. On the other hand, SMV often shows low attenuation because contrast agents do not reach the SMV because of the longer route through entero-mesenteric circulation. In arterial-phase CT, if the areas of lobar hepatic steatosis show significantly decreased contrast enhancement in comparison to the areas of non-fatty liver, this may support the above hypothesis. Therefore, we attempted to evaluate the relationship between the portal flow hemodynamics and lobar hepatic steatosis by comparing the contrast enhancement effects between the areas of lobar hepatic steatosis and non-fatty livers on arterial-phase CT images obtained at the time at which contrast agent was flowing into the SV (high attenuation in the SV) but not yet fully into the SMV (low attenuation in the SMV). Understanding the cause of lobar hepatic steatosis may be an important insight into the pathogenesis of hepatic steatosis. Thus, the purpose of this study was to evaluate the association of portal flow hemodynamics with lobar hepatic steatosis by multiphasic DCE-CT.

2. Materials and methods

2.1. Study population

This retrospective study received institutional review board approval, and the requirement for written informed consent was waived. A search of our radiology database was performed to recruit patients who underwent multiphasic DCE-CT and for who suspected hepatic steatosis was noted on CT reports from July 2015 to June 2020. Hepatic steatosis was defined based on the CT attenuation value of the hepatic parenchyma (<48 HU on unenhanced CT) according to a previous study [5]. Among these patients, we excluded 120 patients due to the following reasons: 1) history of abdominal surgery (n = 65); 2) hepatic lesion > 3 cm in diameter (n = 45); 3) portal vein thrombus (n = 1); and 4) failure of dynamic imaging (n = 9). Additionally, patients in whom the contrast agent was already fully flowing into the SMV on arterial-phase CT, and who showed high attenuation similar to the SV (n = 68), were also excluded. Lobar hepatic steatosis was defined based on a > 10 HU difference in the CT attenuation values of the lobes with hepatic steatosis (<48 HU) and the remaining lobes of on unenhanced CT. Thus, the final study population consisted of 235 patients (male, n = 135; female, n = 100; mean age, 61.8 ± 12.5 years [range, 21–90 years]), 77 with lobar hepatic steatosis, 158 with diffuse hepatic steatosis with (n = 76) and without (n = 82) a focal fatty spared area (Fig. 1).

2.2. CT

Abdominal CT examinations were performed with a MDCT scanner (SOMATOM Definition, Sensation 64 or Force; Siemens Healthineers, Erlangen, Germany, Optima CT660 Pro, GE Healthcare, Tokyo, Japan, or Aquilion Precision; Canon Medical Systems, Otawara, Japan). Patients were required to fast for at least four hours prior to CT examinations. All scans were obtained in the cephalocaudal direction. The CT scanning parameters were optimized for each scanner as follows: tube voltage, 100 or 120 kVp; mAs were automatically adjusted to the patient's body build; field of view (FOV), 35 cm; 512 × 512 matrix; and section collimation, 0.5 – 0.625 mm. All images were reconstructed using an interpolated slice thickness and interval of 1.0 mm. After obtaining an unenhanced CT scan through the liver, triple-phase contrast-enhanced dynamic CT was performed after a bolus injection of almost 600 mg I/kg of nonionic contrast agent (iopamidol [Oypalomin 300 or 370, Konica Minolta, Tokyo, Japan and Iopamiron 370, Bayer, Osaka Japan]; or iohexol [Omnipaque 300, GE Healthcare Pharma, Tokyo Japan]; or iomeprol [Iomeron 300 or 350, Eisai, Tokyo Japan]; or ioversol [Optiray 320, Guerbet Japan, Tokyo Japan]) using a standardized protocol. Contrast agent was administered for 30 s using a power injector (injection rate: 3 to 5 ml/s, depending on the patient's weight). A bolus-tracking technique was used to trigger the hepatic arterial phase scan 22 s after contrast enhancement of the upper abdominal aorta to an attenuation threshold of 100 HU. Portal venous phase and equilibrium phase images were obtained 70 and 180 s, respectively, after the start of injection of the contrast agents.

2.3. Image analyses

Two radiologists with 4 and 11 years of experience in abdominal CT interpretation set a circular or oval region of interest (ROI) on images of the liver to measure the CT attenuation values (Hounsfield unit: HU) of the hepatic parenchyma with and without hepatic steatosis on unenhanced and arterial-phase CT, respectively. The angle between the SV and the SMV which was denoted as the spleno-mesenteric confluence (SMC) angle [6] was also measured on the coronal images reconstructed by using partial maximal intensity projection techniques (Fig. 2). Final verification of the ROI placement and measurement was confirmed by a senior radiologist with 30 years of experience in abdominal imaging. The size of the ROI was at least 100 mm^2 or, in the area of focal fatty sparing, maximized to fit the size. The contrast enhancement values were calculated as the difference in HU values between the unenhanced image and arterial-phase CT image, and were used for the data analysis.

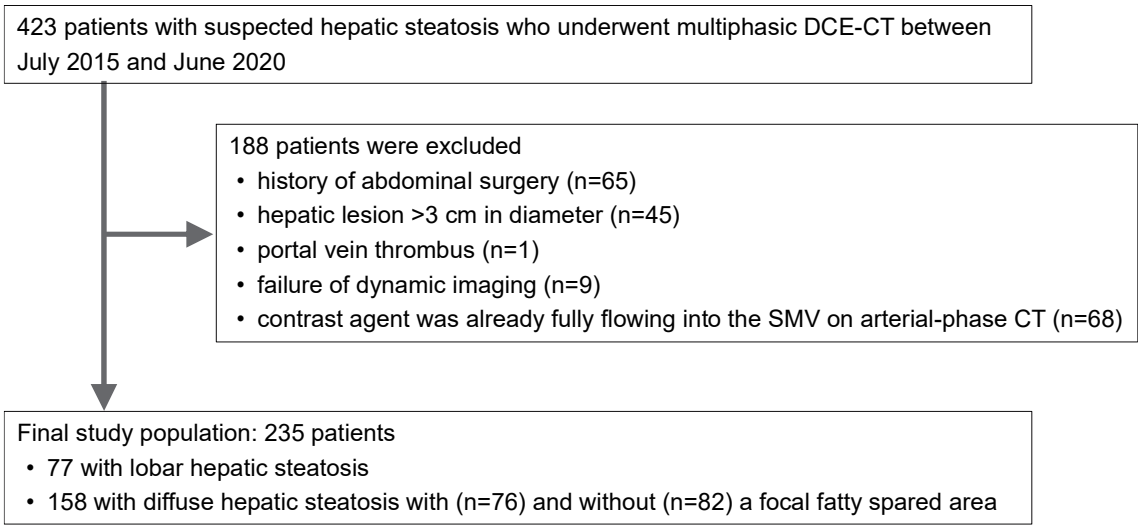

Fig. 1. Flowchart of patient selection.

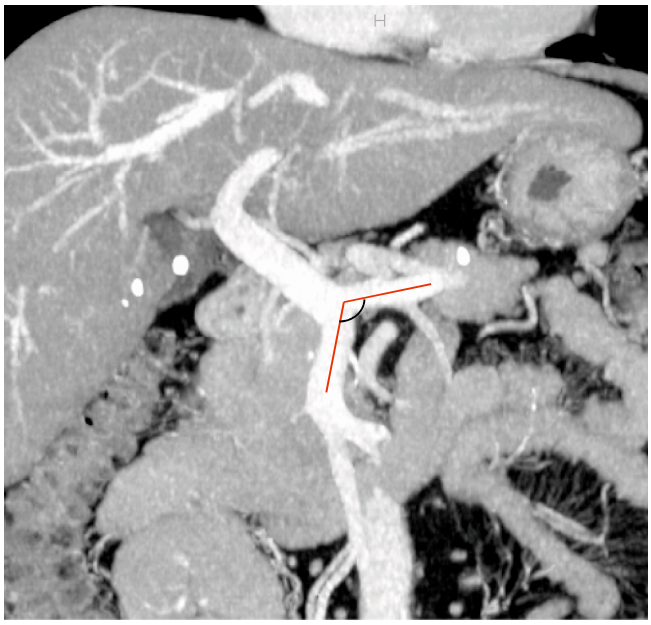

Fig. 2. The spleno-mesenteric confluence (SMC) angle. The angle between the splenic vein and the superior mesenteric vein (SMC angle) was measured on the portal-phase coronal image reconstructed by using partial maximal intensity projection techniques.

These measurements were conducted on a picture archiving and communication system (PACS) workstation (ShadeQuest/ViewR-DG, FUJIFILM Medical Solutions, Tokyo, Japan) where patients' information was anonymized, and CT datasets were randomized for blind-reading purposes. In patients with a focal spared area within diffuse hepatic steatosis, the location was recorded.

2.4. Statistical analyses

All statistical analyses were performed using the JMP Pro software program (version 16; SAS Institute, Cary, North Carolina, USA). The data distribution was assessed using the Shapiro-Wilk test. Quantitative variables were presented as the mean and standard deviation, or the median with 25th and 75th percentiles for non-normally distributed data. Data with abnormal distribution were analyzed using Wilcoxon signed-rank test. Comparison in the SMC angle between the right lobar and left lobar steatosis groups were analyzed using unpaired *t*-test. *P*-values of < 0.05 were considered to indicate a statistically significant difference.

3. Results

Among 77 patients with lobar hepatic steatosis, 67 (87 %) patients had lobar steatosis of the right hepatic lobe (Fig. 3) while 10 (13 %) had lobar steatosis of the left hepatic lobe (Fig. 4). The comparison of the mean contrast enhancement value between the areas of lobar steatosis and the non-fatty lobe in the group with lobar hepatic steatosis is summarized in Table 1. In patients with lobar steatosis of the right hepatic lobe, the median contrast enhancement values of the areas of right lobar steatosis were significantly lower than those of the non-fatty left lobe (13 [IQR 7–19] vs 23 [13–33] HU, $P < 0.01$), suggesting dominant SMV flow to the right lobe with lobar hepatic steatosis. Conversely, in patients with lobar steatosis of the left hepatic lobe, the median contrast enhancement values of the areas of areas of left lobar steatosis (15.5 [11.75–21.5] HU) were lower than those of the non-fatty right lobe (16 [14.5–22] HU), but this difference was not statistically significant ($P = 0.20$) (Fig. 5). Regarding the comparison in the SMC angle between the right lobar and left lobar steatosis groups, the mean SMC angle in the left lobar steatosis group (96.2 ± 11.9) tended to be small, compared with that in the right lobar steatosis group (104.8 ± 16.4) although the difference was not statistically significant (p = 0.098).

In 82 patients with diffuse hepatic steatosis without a focal fatty spared area, the median contrast enhancement values of the right lobe were significantly lower than those of the left lobe (10.5 [4–20] vs 11.5 [7.0–20.3] HU, $P < 0.01$), suggesting dominant SMV flow to the right lobe with diffuse hepatic steatosis (Table 1) (Fig. 5). In these patients, the median CT attenuation values of the right lobe on unenhanced CT were significantly lower than those of the left lobe on unenhanced CT (38.5 [30.75–42] vs 38.5 [33–44.25] HU, $P < 0.01$) although the mean difference in their CT attenuation value was<2 HU (35.4 vs 36.9 HU).

In 76 patients with diffuse hepatic steatosis accompanying a focal fatty spared area, 48 patients had a focal fatty spared area around the gallbladder fossa while it was observed in the posterior aspect of the left medial segment (segment IV) in 28 patients. There were significant differences in the median contrast enhancement values between areas of hepatic steatosis and focal fatty spared areas in the gallbladder fossa

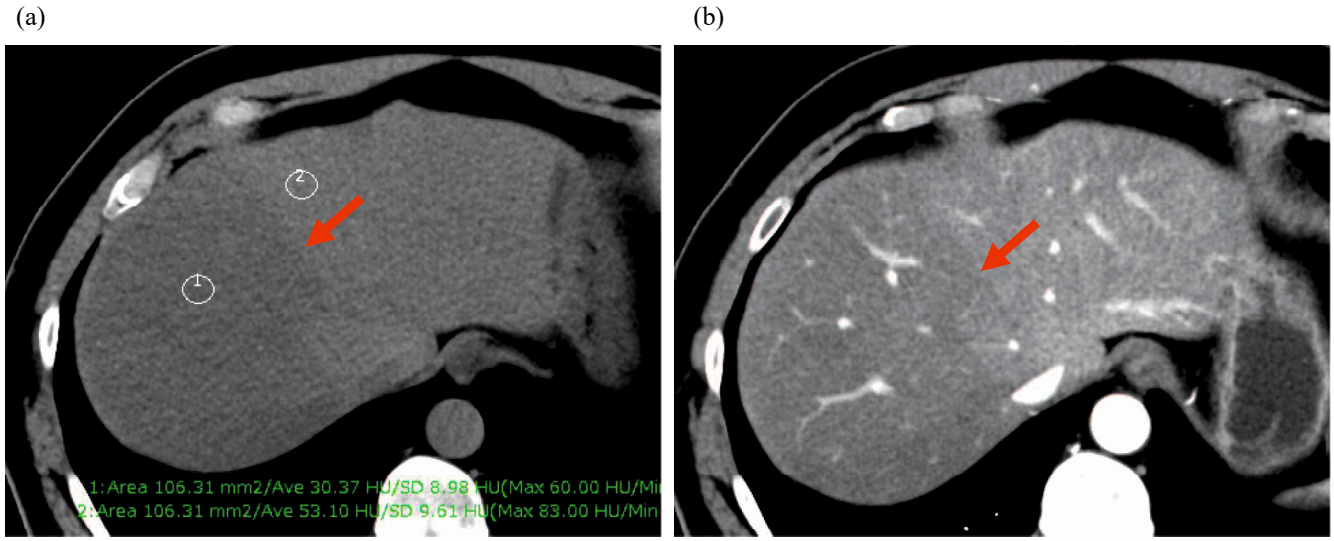

Fig. 3. A 46-year-old man with right lobar steatosis. a) Unenhanced CT and b) arterial-phase CT show hepatic steatosis of the right hepatic lobe with straight boundary (arrows). CT attenuation values of the right and the left hepatic lobe on unenhanced CT were 30.4 and 53.1 HU, respectively. Contrast enhancement value of the areas of right lobar steatosis was lower than that of the non-fatty left lobe.

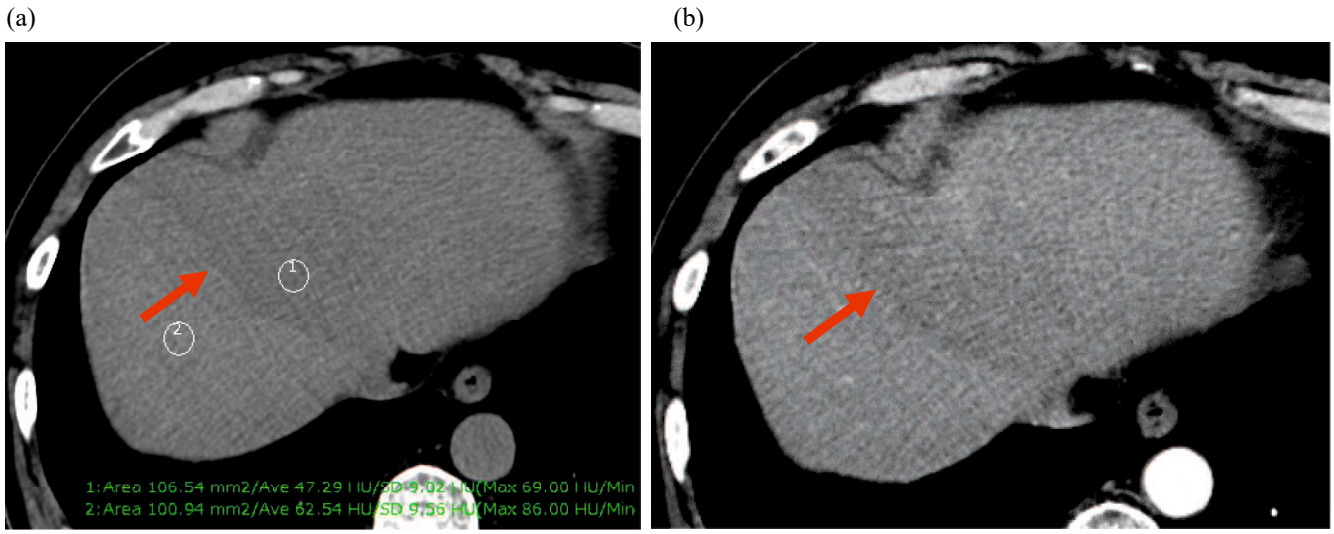

Fig. 4. A 65-year-old man with left lobar steatosis. a) Unenhanced CT and b) arterial-phase CT show predominant hepatic steatosis of the left hepatic lobe (arrows). CT attenuation values of the right and the left hepatic lobe on unenhanced CT were 62.5 and 47.3 HU, respectively. Contrast enhancement value of the areas of left lobar steatosis was slightly lower than that of the non-fatty right lobe.

Table 1
The comparisons of the median contrast enhancement value between the right and left lobe, in patient group with right lobar, left lobar and diffuse hepatic steatosis.

Type of steatosis	Median contrast enhancement values (HU)		
	Right hepatic lobe	Left hepatic lobe	*P*-value
Right lobar steatosis group (n = 67)	13 [7–19]	23[13–33]	< 0.01
Left lobar steatosis group (n = 10)	16 [14.5–22]	15.5 [11.75–21.5]	0.20
Diffuse steatosis group (n = 82)	10.5[4–20]	11.5[7–20.3]	< 0.01

Data represent the median values with the 25th and 75th percentiles.

group (15.5 [9–24.3] vs 17 [8.3–32.5] HU, $P = 0.01$) and in the segment IV group (11 [6–25.5] HU vs 23 [10.3–43.8], $P < 0.01$) (Fig. 6).

4. Discussion

In this study, lobar steatosis was observed in the right hepatic lobe in 67 (87 %) of 77 patients with lobar hepatic steatosis. In these patients, the contrast enhancement values of the steatotic right lobe were significantly lower than those of the non-fatty left lobe. These results indicated that the SMV flow was dominantly distributed to the right lobe with lobar hepatic steatosis, and suggested that the predominant SMV flow may be one of the causes of right lobar hepatic steatosis since the blood flow from the SMV contains abundant lipogenic alimentary factors [3,4], which may result in fatty changes in hepatocytes [7]. Although the difference in the lobar distribution of the blood flow from the SMV and the SV is still controversial, several studies based on angiography and scintigraphy findings have supported the existence of selective portal streamlining by which the SV flow is largely sent to the left liver, and the SMV flow is largely sent to the right liver [8,9]. Therefore, the different portal patterns of the left and right liver might explain the difference in lobar steatosis [10].

Conversely, in 13 % of patients with lobar steatosis of the left hepatic lobe, the contrast enhancement values of areas of left lobar steatosis tended to be lower than those of the non-fatty right lobe, implying that the SMV flow tended to be distributed to the left lobe with lobar hepatic steatosis while the SV flow tended to be sent to the non-fatty right lobe in these patients. In a previous study using unenhanced MR portography with a selective inversion-recovery pulse, the SV flow was distributed to

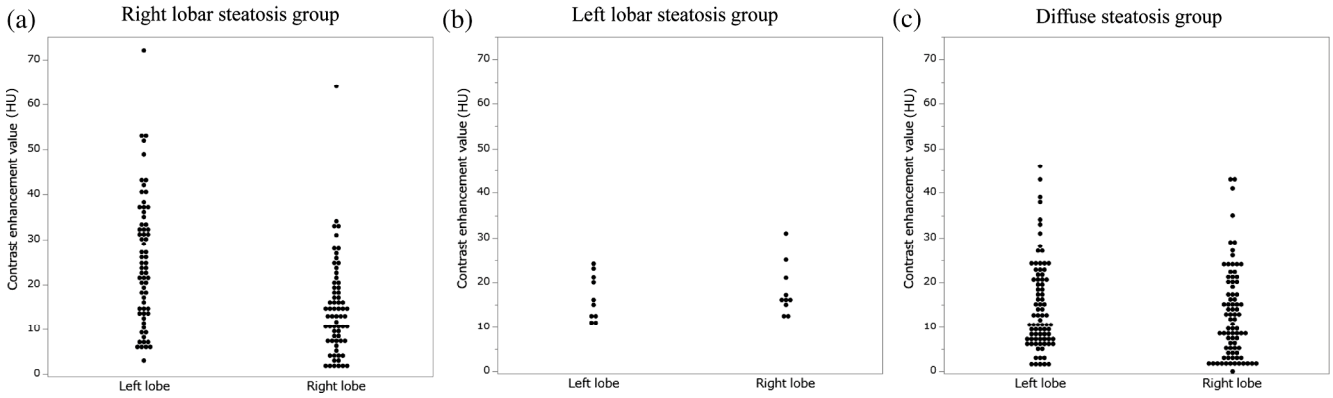

Fig. 5. The comparisons of the median contrast enhancement value between the right and left lobe. a) In the right lobar steatosis group, the median contrast enhancement values of the areas of right lobar steatosis were significantly lower than those of the non-fatty left lobe ($P < 0.01$). b) In the left lobar steatosis group, the median contrast enhancement values of the areas of left lobar steatosis were lower than those of the non-fatty right lobe, but this difference was not statistically significant ($P = 0.20$). c) In the diffuse steatosis group, the median contrast enhancement values of the right lobe were significantly lower than those of the left lobe ($P < 0.01$).

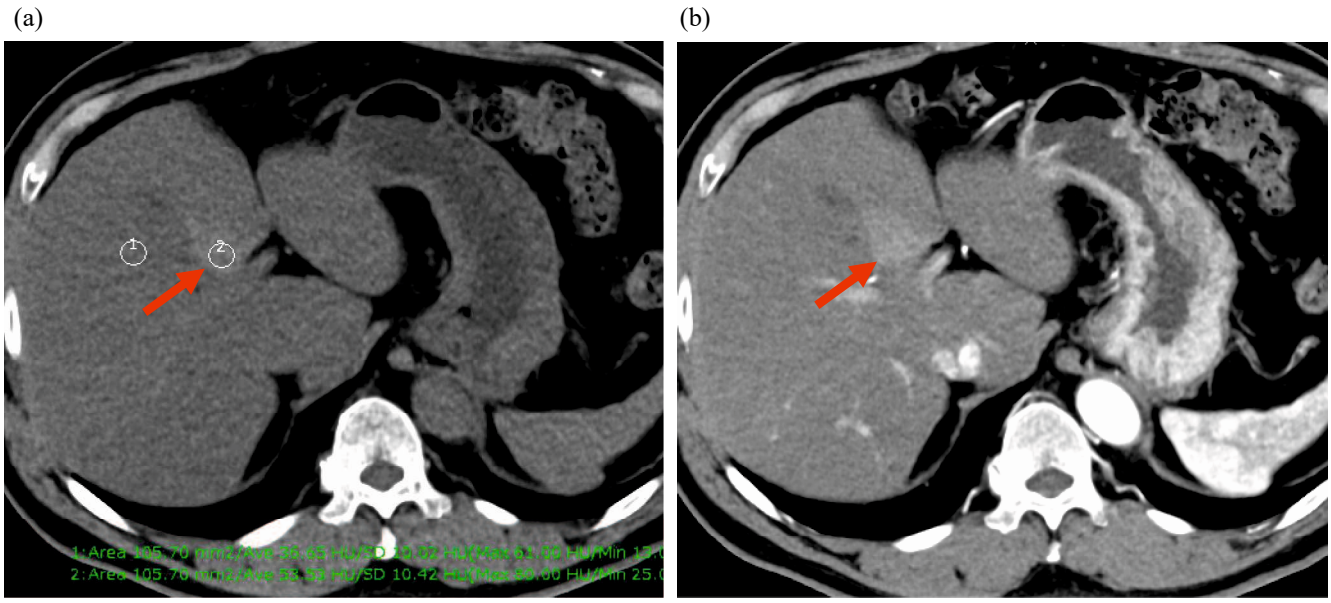

Fig. 6. A 63-year-old man with diffuse hepatic steatosis accompanying a focal fatty spared area. a) Unenhanced CT shows a relatively hyper-attenuating focal area in the posterior aspect of the left medial segment (arrow). CT attenuation values of the focal spared area and the right hepatic lobe were 53.5 and 36.7 HU, respectively. b) Arterial-phase CT. Contrast enhancement value of focal fatty spared areas was higher than that of the areas of hepatic steatosis.

the right side of the portal vein in 10 % of the patients [11], similar to the frequency of our results showing dominant SV flow in the right hepatic lobe. An experimental study by Barnett et al. [12], using a model formed by a tributary stream joining the main stream, suggested that the SV flow (i.e., the tributary stream) may pass across the portal vein (i.e., the main stream), and preferentially distribute to the right lobe when the SV flow is increased. Additionally, another study also reported that an increase in the percentage of SMV flow to the left portal vein was strongly correlated with the helicity of portal flow [6]. This previous study analyzed the effects of the portal helix on hemodynamic metrics and blood flow distributions, and examined the influence of the splenomesenteric confluence (SMC) angle and configuration on flow distribution and the development of helical flow. It showed that the degree of portal helical flow formation can be significantly correlated with the SMC orientation, and that the lobe-specific portal flow distribution was significantly affected by the geometry of the SMC. For instance, the percentage of flow to the left portal vein from the SV decreased when SMC angle was decreased and the amount of flow traveling from the SMV to the left portal vein tended to increase. In our study, the SMC angle tended to be decreased in patients with left lobar steatosis, compared with patients with right lobar steatosis, supporting the previous study although the difference was not significant. Additionally, the flow distribution between the right and left portal venous branches were significantly correlated with the degree of helicity in the portal vein, although there may be some variations among human subjects. Therefore, we should note that there will be several factors involved that govern these portal flow dynamics and distributional relationships (angle, orientation, and configuration of SMC, and helicity of the portal flow).

The present study also showed that contrast enhancement values in the right liver were increased in comparison to those in the left liver, even in patients with diffuse steatosis without a focal fatty spared area. In these patients, a higher amount of steatosis was observed in the right hepatic lobe, in comparison to the left lobe, although the difference was minimal. Additionally, in these patients, the contrast enhancement values of both the right and left lobe were lower than those in patients with lobar steatosis. These facts suggested that both lobes are strongly affected by the SMV flow in patients with diffuse steatosis, but the right lobe was more susceptible to the physiological streamlined SMV flow. Furthermore, alteration in the portal blood mixture from the SV and SMV with different blood composition can cause significant changes in the pattern of portal flow distribution, potentially leading to maldistribution in hepatic steatosis. Therefore, understanding the pathophysiology and hemodynamics in the lobar or segmental heterogeneity of steatosis would be critical for correctly evaluating the severity and progression of hepatic steatosis.

Regarding focal fatty sparing within diffuse hepatic steatosis, focal fatty spared areas around the gallbladder fossa and the posterior aspect of left medial segment (segment IV) have been reported to be caused by non-portal venous return from the cystic veins and aberrant gastric veins [7,13–15]. Decreased portal inflow due to non-portal blood supply (so-called “third inflow”) via these venous drainages may explain why these areas were spared from steatosis.

The present study was associated with some limitations. First, our study population may have resulted in selection bias since patients who showed high attenuation in the SMV were excluded, and the anatomical variation of portal vein (e.g., a true portal trifurcation) was not considered. Second, histological confirmation of the degree of hepatic steatosis was not obtained. Liver biopsy may be still considered the reference standard for quantifying the liver fat content. However, biopsy is not appropriate as a screening tool for hepatic steatosis since it is invasive, it may suffer from sampling errors and variability [16], and biopsy samples represent only 1/50,000–1/65,000 of the whole liver [17]. Third, we used a cutoff value of < 48 HU for steatosis with high diagnostic specificity for moderate to severe steatosis [5]. However, there is concern that this cutoff value did not include mild hepatic steatosis and may have resulted in a population bias. Therefore, our results require further confirmation in a larger population that includes patients with mild hepatic steatosis. Fourth, five different CT scanners were used; however, the imaging parameters have been optimized for each scanner, and the contrast-enhanced protocol has been standardized across all scanners. Fifth, since CT examinations were performed in the fasting state, the blood flow distribution may differ from that after a meal, which contains a large amount of fatty components. However, contrast-enhanced CT after food intake is not recommended due to the risk of aspiration. Finally, this study did not take into account the SMC angle, orientation, or configuration, which could affect portal flow distribution and helical flow development. In a future study, it will be

necessary to consider these factors in relation to lobar hepatic steatosis and hemodynamic changes of the portal flow.

In conclusion, lobar hepatic steatosis may be associated with regional changes of the portal flow hemodynamics (i.e., predominant perfusion from the SMV flow to the lobes with steatosis). Understanding the mechanism through which lobar hepatic steatosis is related to regional changes of portal flow hemodynamics will be an important insight into the pathogenesis of hepatic steatosis.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

Funding

This study was not supported by any funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Z.M. Younossi, A.B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, M. Wymer, Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes, Hepatology 64 (2016) 73–84, https://doi.org/10.1002/hep.28431.

[2] R. Kumar, R.N. Priyadarshi, U. Anand, Non-alcoholic Fatty Liver Disease: Growing Burden, Adverse Outcomes and Associations, J Clin Transl Hepatol 8 (2020) 76–86, https://doi.org/10.14218/JCTH.2019.00051.

[3] P.O. Decarie, L. Lepanto, J.S. Billiard, D. Olivie, J. Murphy-Lavallee, C. Kauffmann, A. Tang, Fatty liver deposition and sparing: a pictorial review, Insights into imaging 2 (2011) 533–538, https://doi.org/10.1007/s13244-011-0112-5.

[4] D. Mathieu, A. Luciani, A. Achab, B. Zegai, M. Bouanane, H. Kobeiter, Hepatic pseudolesions, Gastroenterol. Clin. Biol. 25 (2001) B158–B166.

[5] P.J. Pickhardt, S.H. Park, L. Hahn, S.G. Lee, K.T. Bae, E.S. Yu, Specificity of unenhanced CT for non-invasive diagnosis of hepatic steatosis: implications for the investigation of the natural history of incidental steatosis, Eur. Radiol. 22 (2012) 1075–1082, https://doi.org/10.1007/s00330-011-2349-2.

[6] D.R. Rutkowski, R. Medero, F.J. Garcia, A. Roldan-Alzate, MRI-based modeling of spleno-mesenteric confluence flow, J. Biomech. 88 (2019) 95–103, https://doi.org/10.1016/j.jbiomech.2019.03.025.

[7] K. Yoshimitsu, H. Honda, T. Kuroiwa, H. Irie, H. Aibe, K. Shinozaki, K. Masuda, Unusual hemodynamics and pseudolesions of the noncirrhotic liver at CT, Radiographics : a review publication of the Radiological Society of North America, Inc 21 Spec No 27 (2001), https://doi.org/10.1148/radiographics.21.suppl_1.g01oc06s81. S81-96.

[8] B. Barbaro, G. Palazzoni, R. Prudenzano, A. Cina, R. Manfredi, P. Marano, Doppler sonographic assessment of functional response of the right and left portal venous branches to a meal, J. clin. ultrasound : JCU 27 (1999) 75–80, https://doi.org/10.1002/(sici)1097-0096(199902)27:2<75::aid-jcu5>3.0.co;2-f.

[9] G.F. Gates, E.K. Dore, Streamline flow in the human portal vein, Journal of nuclear medicine : official publication, Society of, Nuclear Med. 14 (1973) 79–83.

[10] V. Capitan, J.M. Petit, S. Aho, P.H. Lefevre, S. Favelier, R. Loffroy, P. Hillon, D. Krause, J.P. Cercueil, B. Guiu, Macroscopic heterogeneity of liver fat: an MR-based study in type-2 diabetic patients, Eur. Radiol. 22 (2012) 2161–2168, https://doi.org/10.1007/s00330-012-2468-4.

[11] T. Tsukuda, K. Ito, S. Koike, K. Sasaki, A. Shimizu, T. Fujita, M. Miyazaki, H. Kanazawa, C. Jo, N. Matsunaga, Pre- and postprandial alterations of portal venous flow: evaluation with single breath-hold three-dimensional half-Fourier fast spin-echo MR imaging and a selective inversion recovery tagging pulse, J. Magn. Reson. Imaging 22 (2005) 527–533, https://doi.org/10.1002/jmri.20419.

[12] C.H. Barnett, W. Cochrane, Flow of viscous liquids in branched tubes with reference to the hepatic portal vein, Nature 177 (1956) 740–742, https://doi.org/10.1038/177740a0.

[13] O. Matsui, M. Kadoya, S. Takahashi, J. Yoshikawa, T. Gabata, T. Takashima, K. Kitagawa, Focal sparing of segment IV in fatty livers shown by sonography and CT: correlation with aberrant gastric venous drainage, AJR Am. J. Roentgenol. 164 (1995) 1137–1140, https://doi.org/10.2214/ajr.164.5.7717220.

[14] K. Ito, T. Choji, T. Fujita, T. Matsumoto, T. Nakada, T. Nakanishi, Early-enhancing pseudolesion in medial segment of left hepatic lobe detected with multisection dynamic MR, Radiology 187 (1993) 695–699, https://doi.org/10.1148/radiology.187.3.8497615.

[15] K. Ito, H. Awaya, D.G. Mitchell, K. Honjo, T. Fujita, H. Uchisako, K. Moritani, S. Nomura, M. Higuchi, T. Kada, T. Matsumoto, N. Matsunaga, Gallbladder disease: appearance of associated transient increased attenuation in the liver at biphasic, contrast-enhanced dynamic CT, Radiology 204 (1997) 723–728, https://doi.org/10.1148/radiology.204.3.9280250.

[16] V. Ratziu, F. Charlotte, A. Heurtier, S. Gombert, P. Giral, E. Bruckert, A. Grimaldi, F. Capron, T. Poynard, L.S. Group, Sampling variability of liver biopsy in nonalcoholic fatty liver disease, Gastroenterology 128 (2005) 1898–1906, https://doi.org/10.1053/j.gastro.2005.03.084.

[17] E.M. Brunt, D.G. Tiniakos, Histopathology of nonalcoholic fatty liver disease, World J. Gastroenterol. 16 (2010) 5286–5296, https://doi.org/10.3748/wjg.v16.i42.5286.