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FULL PAPER

The evaluation of haemodynamics in cirrhotic patients with spectral CT

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Objective: To evaluate haemodynamics in cirrhotic patients with portal hypertension using spectral CT imaging.

Methods: 118 cirrhotic patients with portal hypertension were included in the study group (further divided into Child-Pugh A, B and C subgroups). The control group consisted of 21 subjects with normal liver functionality. All subjects underwent three-phase spectral CT scans. Material decomposition images with water and iodine as basis material pairs were reconstructed. The iodine concentrations for the hepatic parenchyma in both arterial and portal venous phases were measured. The arterial iodine fraction (AIF) was obtained by dividing the iodine concentration in the hepatic arterial phase by that in the portal venous phase. AIF values from the study and control groups were compared using analysis of

variance and between subgroups using a *post-hoc* test with Bonferroni correction, with a statistical significance of $p < 0.05$.

Results: The AIF was 0.25 ± 0.05 in the control group, and 0.29 ± 0.10 , 0.37 ± 0.12 and 0.43 ± 0.14 in the study group with Child-Pugh Grades A, B and C, respectively. The difference in AIF between the control and study groups was statistically significant. The differences were statistically significant between the subgroups with multiple comparisons except between the control group and the Child-Pugh A group ($p = 0.685$).

Conclusion: AIF measured in spectral CT could be used to evaluate the liver haemodynamics of cirrhotic patients.

Advances in knowledge: The AIF, provided by spectral CT, could be used as a new parameter to observe liver haemodynamics.

Portal hypertension in patients with hepatic cirrhosis usually leads to changes in not only liver morphology but also liver perfusion and haemodynamics [1]. At present, a CT liver perfusion scan is one of the imaging means to obtain liver haemodynamics. Perfusion parameters, such as liver blood volume, blood flow (BF), mean transit time (MTT) and hepatic perfusion index (HPI), can be obtained by perfusion scans using the cine mode or dynamic shuttle mode and mathematic calculations [2–4]. Liver haemodynamic changes in cirrhotic patients with portal hypertension can be detected by calculating the liver perfusion parameters, including decreasing liver BF and increasing liver HPI, that are related to decreased liver function [1,5].

However, some drawbacks of CT liver perfusion scan limit its clinical usefulness. Many patients cannot endure the long breath-hold time necessary for perfusion scans. As a result, motion artefacts often occur [6–8]. Another concern is the relatively high radiation dosage involved in cine scans [9–11]. As a substitutional method for obtaining CT liver perfusion parameters, an arterial enhancement fraction

(AEF) parameter was calculated from a simulated multiphasic liver CT by Kim et al [12], which was found to correlate strongly with HPI measured with perfusion CT.

Recently, a new CT scanning mode, the spectral CT mode, was introduced. This scanning mode is based on the single tube fast switching between low (80 kV) and high (140 kV) energy data sets. Spectral CT produces both monochromatic and material decomposition image sets [13]. One of the properties of spectral CT is that it enables accurate assessment of the concentration of certain materials, such as iodine, the active ingredient of contrast medium, in tissues or tumours [14]. The liver has two sets of blood systems, the hepatic artery and the portal vein blood supply. In contrast-enhanced CT, liver density changes in the hepatic arterial and portal venous phases reflect the hepatic artery and portal vein perfusion. A previous study using an animal model has indicated that there is a close correlation between liver blood perfusion parameters HPI and the iodine concentration ratio in the hepatic arterial and portal venous

phases in the hepatic parenchyma [hepatic arterial iodine fraction (AIF)] after contrast injection [15]. The objective of this study was to compare the AIF obtained in spectral CT imaging of cirrhotic patients with portal hypertension to that of the control group with normal liver functionality and to evaluate the possibility of estimating the liver haemodynamics of cirrhotic patients using the AIF.

MATERIALS AND METHODS

Study population

Approval for this retrospective study was obtained from the institutional review board of our hospital. 118 consecutive cirrhotic patients who underwent liver spectral CT examination from October 2010 to March 2012 were enrolled in our study retrospectively. All patients had clinically confirmed cirrhosis with portal hypertension by clinical history, laboratory, ultrasound or MRI, and were definitively diagnosed with cirrhosis according to the Viral Hepatitis Prevention and Control Programs in China [16]. All patients underwent CT examination with the aim of evaluating the hepatic abnormality and the status of portal-systemic circulation. There were 78 males and 40 females aged between 33 and 84 years (mean age 59.21 ± 10.8 years). The severity of the cirrhosis was evaluated using the Child–Pugh classification. There were 42 patients in Child–Pugh Grade A, 48 in Grade B and 28 in Grade C. These cases included 69 of cirrhosis after hepatitis B, 8 of cirrhosis after hepatitis C, 28 of alcoholic cirrhosis, 8 of primary biliary cirrhosis, 3 of drug cirrhosis and 2 of immunity cirrhosis. Patients who had a suspected liver tumour on CT and were diagnosed as having hepatocellular carcinoma in the ultrasound follow-up testing 3 months after the CT examination were ruled out.

21 consecutive patients were included in the control group. The inclusion criteria for the control group were as follows: normal liver function and haemodynamics, no prior liver disease (such as hepatitis B or C), no history of alcohol consumption and no evidence of portal vein thrombosis. These patients underwent spectral CT for suspected liver lesions by ultrasound. There were 15 males and 6 females in this control group, aged between 36 and 71 years (mean age 51.12 ± 12.61 years).

Imaging technique

All patients underwent routine three-phasic (plain, arterial and portal venous phases) spectral CT scans on a Discovery™ CT750 HD scanner (GE Healthcare, Wauwatosa, WI) using a single-tube, fast-dual tube potential (80 kVp and 140 kVp) switching scan technique. The scan coverage was from the diaphragmatic dome to the lower poles of both kidneys. Other scan parameters included 40-mm detector coverage, helical with a pitch factor of 0.985:1, 0.8-s tube rotation time and auto mA for a CT dose index volume of 25.8 mGy for a single phase, which was similar to the dose on the conventional contrast-enhanced liver scans for an average-sized patient in our institution. The images were reconstructed with 5-mm slice thickness and a 35-cm display field of view. The non-ionic contrast medium Iohexol (Omnipaque™ 350, GE Healthcare, Shanghai, China) at a dose of 500 mgI kg^{-1} body weight (1.4 mL kg^{-1}) was injected in 30 s with a power injector through the median cubital vein. The injection rate was between 4.0 mL s^{-1} and 5.0 mL s^{-1} . The hepatic arterial phase (HAP) scans were triggered 20 s after the attenuation in the descending aorta reached 100 HU on the monitoring scan. The portal venous phase (PVP) scans began 30 s after the end of the HAP scan.

Data processing

Two types of images were reconstructed from a single spectral CT acquisition for analysis: water- and iodine-based material decomposition images and 101 sets of monochromatic images from 40 keV to 140 keV. The iodine-based material decomposition images were analysed on an advanced workstation (AW4.4; GE Healthcare, Waukesha, WI) for the iodine content in the liver parenchyma using the Gemstone Spectral Imaging Viewer software package (GE Healthcare, Waukesha). A circular region of interest (ROI) of approximately 200 mm^2 was placed on both the right posterior and the left median liver lobe parenchyma on the main stem of the portal vein right branch slices with caution, avoiding the large vessels in the HAP (Figure 1A) and PVP (Figure 1B), to measure the iodine concentration. The values from the two ROIs in each phase were averaged to represent the mean iodine concentration. The AIF was calculated using the following formula: $\text{AIF} = \text{iodine concentration (HAP)} / \text{iodine concentration (PVP)}$.

Figure 1. Iodine concentration measurement in the liver parenchyma in the hepatic artery phase (HAP) and portal venous phase (PVP). (a) In the HAP, on an iodine-based material decomposition image reconstructed with a high-definition CT spectral software package, a circular region of interest (ROI) with an area of approximately 200 mm^2 was placed on both the right posterior and the left median liver lobes on the slice with the largest liver parenchyma, avoiding the large vessels. (b) In the PVP, an ROI with a similar area and location as that in the HAP was used on the iodine-based material decomposition image.

Table 1. Comparisons of AIF in different liver lobes for the study and control groups

Groups	AIF-l	AIF-r	<i>t</i> -value	<i>p</i> -value
Control group	0.25 (0.04)	0.25 (0.04)	2.21	0.16
Child–Pugh A group	0.28 (0.11)	0.29 (0.10)	0.62	0.54
Child–Pugh B group	0.36 (0.12)	0.37 (0.12)	0.78	0.44
Child–Pugh C group	0.43 (0.13)	0.43 (0.14)	0.20	0.85

AIF-l, the AIF value of the left liver lobe; AIF-r, the AIF value of the right liver lobe.

Statistical analyses

Statistical analysis was carried out using SPSS® v. 13 (SPSS, Inc., Chicago, IL). A paired *t*-test was used to analyse the differences in AIF between the right posterior and left median liver lobe parenchyma of all patients. The AIF between the study group of different Child–Pugh grades and the control group was then compared using analysis of variance and between subgroups using a *post-hoc* test with Bonferroni correction with a statistical significance of $p < 0.05$.

RESULTS

The AIF values calculated using the iodine concentration measured from the right posterior and left median liver lobes separately in different groups are listed in Table 1. There was no statistical difference between the AIF values from the two liver lobes in all groups. The average iodine concentrations in liver parenchyma from the two lobes in the HAP and PVP and the resulting AIF values for patients in the study group of different Child–Pugh grades and in the control group are listed in Table 2 and Figure 2. The iodine concentration in the PVP was higher than that in the HAP in both the study and control groups. However, in the HAP, the liver parenchyma iodine concentration of the study group was slightly higher than that of the control group. In the PVP, it was lower than that of the control group. The AIF values increased with increasing Child–Pugh grades in the study group. There were statistical differences for AIF between the control group and the Child–Pugh B and C grades in the study group (both $p = 0.001$). Also, there were differences in the AIF between Child–Pugh A and B groups ($p = 0.001$), Child–Pugh A and C groups ($p < 0.001$) and Child–Pugh B and C groups ($p = 0.01$), but no difference for the normal and Child–Pugh A groups ($p = 0.14$) (Table 2).

Paired comparison of iodine concentration between the control and study groups is shown in Table 3. Group I

indicates any one subgroup, and Group J indicates any other subgroups that have not been used to be compared with Group I.

DISCUSSION

The haemodynamic changes of cirrhosis with portal hypertension include the formation of collateral circulation between the portal and systemic systems, and changes in perfusion of the liver and other various organs. The liver perfusion condition is informative for patient management and evaluation of progress [3,4]. The HPI, which is the ratio of hepatic arterial perfusion to that of total perfusion, is one of the most commonly obtained hepatic CT perfusion parameters [17]. The normal value of HPI varies according to different reports [5,18], which perhaps is a result of the different mathematic models, scanners or patient selections involved. However, in general, the normal value of HPI is between 1/4 and 1/3.

Relatively high radiation in CT perfusion is a concern and attempts have been made to find alternatives to correlate the perfusion parameters. According to the study by Kim et al [12], the AEF, which was obtained by calculating the ratio of liver parenchyma attenuation (CT value) between the HAP and the PVP [12], was found to correlate to the changes of HPI in both cirrhotic and hepatic tumours. However, CT number in AEF was determined with a polychromatic X-ray source, and different tube voltages produced different average X-ray energies to generate different CT numbers of the same material as well as being more susceptible to beam hardening artefacts [19]. In our study, we attempted to overcome these obstacles by using the spectral CT imaging mode. One of the advantages of spectral CT is the ability to generate material decomposition images for accurate concentration measurement of materials such as iodine [13]. In spectral CT, material decomposition images are reconstructed from projections created through the material

Table 2. The iodine content in the arterial and portal venous phases (mgI ml^{-1}) and AIF for the study and control groups

Groups	Iodine_a (SD) (mgI ml^{-1})	Iodine_pv (SD) (mgI ml^{-1})	AIF (SD)
Control group	0.90 (0.22)	3.41 (0.59)	0.25 (0.04)
Child–Pugh A group	0.84 (0.39)	2.91 (0.58)	0.29 (0.10)
Child–Pugh B group	1.05 (0.38)	2.77 (0.53)	0.37 (0.12)
Child–Pugh C group	1.20 (0.48)	1.20 (0.48)	0.43 (0.14)
<i>F</i> -value			15.78
<i>p</i> -value			0.00

AIF, arterial iodine fraction; Iodine_a, iodine content in the arterial phase; Iodine_pv, iodine content in the portal venous phase; SD, standard variation.

Figure 2. Box plot of healthy and cirrhotic patients of different Child-Pugh grades.

decomposition of the low (80-kVp) and high (140-kVp) projections and represent the amount or density of two materials that would be needed to produce the measured attenuation in the 80-kVp and 140-kVp projections. Iodine is the main component of contrast medium. By using water and iodine as the base material pair and by measuring the iodine content on the iodine-based images obtained by spectral CT scans, the quantity of iodine uptake can be accurately measured, and the blood supply to the liver parenchyma can be directly expressed. The iodine content measured with spectral CT in HAP is proportional to the arterial BF, and that in the PVP is mainly proportional to the whole liver BF. Theoretically, the AIF would then reflect the ratio of the hepatic arterial BF to that of the total liver flow. AIF was obtained based on the iodine concentration in mg mL^{-1} . Similar to AEF, cine-CT scans was not required to obtain the AIF, so additional radiation exposure to patients could be avoided. However, AIF has certain advantages over AEF. The iodine concentration obtained by spectral CT, which is used to calculate AIF, is independent of the scanning techniques, whereas CT numbers in AEF depend strongly on the tube voltages used, and to some extent, on the different scanners used. This tube voltage and/or scanner-dependent phenomenon for CT numbers could be largely avoided with iodine concentration measurement, which

makes accurate quantification possible. The value of AIF in patients with normal liver functionality in the control group was 0.25, which was in the range of normal HPI values reported [5,17]. It indicated that perhaps there was a good correlation between AIF and HPI. The correlation and consistency between AIF obtained by energy spectral CT and HPI obtained by hepatic perfusion CT scan was also demonstrated by our previous study in an animal experiment [15].

The HPI value in cirrhotic patients measured with CT perfusion scan usually increases in some degree because of the hepatic arterial buffer effect [5,8,20]. The haemodynamics of cirrhosis was relevant to its pathology. In cirrhosis, the collapse of the hepatic lobule, diffuse fabric formation and the increase in the collagen component (from a normal level of 4% to 15–30%) made the portal vein and its branches in the liver parenchyma distorted and decreased. The portal vein pressure increased to 20–30 mmHg from a normal 6–10 mmHg and portal hypertension occurred. The backflow of portal vein to liver was hindered, then the perfusion of portal vein decreased and that of the hepatic artery increased. Thus the percentage of hepatic arterial perfusion was raised and HPI increased. Considering AEF indirectly reflects the ratio of hepatic arterial perfusion to total perfusion, it also relates to HPI. Similarly, in our study, the iodine concentration in hepatic parenchyma was found to be higher in the HAP and lower in the PVP for patients in the study group than in the control group, resulting in an elevated AIF for cirrhotic patients with portal hypertension. This value was significantly higher than that for patients with normal liver functions. For the different Child-Pugh grades, our study demonstrated that AIF increased as liver function (Child-Pugh grade) deteriorated in the study group, which may be a result of the increased arterial supply and decreased portal supply of the liver parenchyma in advanced liver cirrhosis [21]. AIF could be a successful predictive indicator for liver haemodynamics of cirrhosis patients when used as a quantitative parameter because it reflects changes in haemodynamics and correlates with Child-Pugh grade.

The timing of the HAP and PVP is a crucial factor in this study to ensure accurate and consistent results. If the HAP acquisition begins too early, the iodine content of the liver parenchyma measured would be lower owing to insufficient hepatic arterial infusion [12]. However, if the acquisition begins too late, iodine

Table 3. Paired comparison of iodine concentration between a control group and patients with cirrhosis of different Child-Pugh grades

Group I	Group J	Mean difference (I–J)	SE	<i>p</i>	95% CI
Normal	Child-Pugh A	–0.04	0.03	0.164	–0.10 to 0.02
	Child-Pugh B	–0.12 ^a	0.03	0.000	–0.18 to –0.06
	Child-Pugh C	–0.16 ^a	0.03	0.001	–0.25 to –0.12
Child-Pugh A	Child-Pugh B	–0.08 ^a	0.02	0.001	–0.12 to –0.03
	Child-Pugh C	–0.14 ^a	0.03	0.000	–0.20 to –0.09
Child-Pugh B	Child-Pugh C	–0.07 ^a	0.03	0.012	–0.12 to –0.01

CI, confidence intervals; SE, standard error.

^aThe mean difference is significant at the 0.05 level.

content measured would probably be higher owing to the participating portal venous infusion. In addition, the iodine concentration measurement could be affected by several factors, such as the dose, concentration and injection rate of iodine contrast material [22]. According to the study by Foley et al [23], the liver parenchyma was well infused by the arterial blood dominative supply and no hepatic venous enhancement in the late arterial phase, which starts approximately 30 s after the initiation of the contrast bolus and lasts for about 12 s. Therefore, the HAP acquisition should be within the late arterial phase to ensure adequate arterial infusion to the liver parenchyma. Yamaguchi et al [24] indicated the optimal delay time of peak hepatic HAP as 19–21 s after the trigger threshold under certain contrast medium infusion conditions by pharmacokinetic analysis and clinical analysis. In fact, the threshold trigger in Yamaguchi et al protocol ensures that the HAP acquisition is accomplished exactly during the late arterial phase. According to the pharmacokinetic principle associated with physiological factors, the time for contrast medium to travel from the median cubical vein to the superior vena cava is 4–5 s, and the mean heart transient time is 10 s. If the scan monitoring delay time (time after the density of the descending aorta reaches 100 HU on the monitoring scan) is set to 20 s for HAP and a 30-s additional delay for PVP after HAP, there will be an approximately 35-s and 65-s scan delay for HAP and PVP scans, respectively; these are consistent with previous reports [24,25]. The contrast medium injection protocol was adopted in this study.

There were several limitations to our study. First, this investigation reflects our preliminary experience with a relative small number of liver cirrhosis patients. Second, even though our study showed that the numerical value of AIF was similar to the perfusion parameter HPI reported in the references, the exact correlation and the consistency between the AIF and the HPI is

still unknown and should be further studied. Also, there is a lot of information which cannot be obtained by static spectral CT but which can be acquired with perfusion CT, such as hepatic perfusion flow, hepatic perfusion volume MTT and permeability surface, which could reflect the liver haemodynamics from different views. Furthermore, spectral CT reflects the amount of iodine in the liver at a certain time point, but perfusion CT can provide information on changes in the liver iodine at multiple time points. Third, for our study, we used the first-generation spectral CT scanning protocol and filtered back projection reconstruction algorithm, which required the use of a normal X-ray dose for the study. Radiation dose reductions of >30% for spectral CT examinations are available on the second generation spectral CT with the use of new spectral CT scan protocols and an adaptive statistical iterative reconstruction algorithm.

CONCLUSIONS

The arterial iodine fraction could be conveniently obtained by measuring the iodine concentrations in the HAP and PVP with spectral CT in routine liver CT scans, which may be used to evaluate the liver haemodynamics of cirrhotic patients.

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