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MDCT = Multi-detector Computed Tomography

Hepatic Enhancement in Multiphasic Contrast-Enhanced MDCT: Comparison of High- and Low-Iodine-Concentration Contrast Medium in Same Patients with Chronic Liver Disease

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100 mL x 300 mg/mL =
30,000 mg = 30 grams!!
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100 mL x 370 mg/mL =
37,000 mg = 37 grams!

OBJECTIVE. The aim of this study was to evaluate the degree of hepatic enhancement and image quality in patients with cirrhosis or chronic hepatitis who underwent multiphasic contrast-enhanced dynamic imaging on MDCT at least twice using standard (300 mg I/mL) and higher (370 mg I/mL) iodine concentrations in contrast medium during follow-up periods.

MATERIALS AND METHODS. This study included 20 patients with chronic liver diseases who underwent at least two multiphasic contrast-enhanced dynamic MDCT examinations using 100 mL of standard (300 mg I/mL = group A) and higher (370 mg I/mL = group B) iodine concentrations in contrast medium. After we obtained unenhanced CT scans, we performed multiphasic scanning at 30 sec (arterial phase), 60 sec (portal phase), and 180 sec (late phase) after the start of contrast medium injection. The CT values of hepatic parenchyma, abdominal aorta, and portal vein were measured. The mean enhancement value was defined as the difference in CT values between unenhanced and contrast-enhanced images. Visual image quality was also assessed on the basis of the degree of hepatic and vascular enhancement, rated on a 4-point scale.

RESULTS. The mean hepatic parenchyma enhancement values in group B was significantly greater ($p < 0.001$) than those in group A during the portal phase (43.8 ± 8.2 H vs 36.2 ± 7.3 H) and the late phase (33.7 ± 7.0 H vs 27.3 ± 3.9 H), but the difference on the arterial phase images between the two groups (9.4 ± 3.2 H vs 8.3 ± 2.5 H) was not significant. The mean aorta-to-liver contrast during the arterial phase in group B was significantly higher ($p < 0.001$) than that in group A (236 ± 40 H vs 193 ± 32 H). For qualitative analysis, the mean visual scores for hepatic parenchyma and vasculature enhancement in group B were significantly higher than those in group A in arterial phase ($p < 0.018$), portal phase ($p < 0.0001$), and late phase ($p < 0.0001$).

CONCLUSION. In the same patients with chronic liver diseases, a higher iodine concentration (370 mg I/mL) in the contrast medium improves contrast enhancement of liver parenchyma in the portal phase and late phase images, improves overall image quality, and helps improve diagnostic accuracy for liver diseases on multiphasic contrast-enhanced dynamic MDCT.

Multiphasic contrast-enhanced dynamic CT of the whole liver has played an important role as a screening examination for patients with cirrhosis or chronic hepatitis because hepatocellular carcinomas (HCCs) or premalignant nodules such as dysplastic nodules frequently develop in cirrhotic livers. Although classic HCCs are commonly hypervascular and tend to be seen best during the arterial phase of contrast enhancement, some well-differentiated HCCs or dysplastic nodules are relatively hypovascular and often can be seen only on late phase images [1, 2]. One study reported the value of adding late phase imaging to dual (arterial and portal) phase helical CT for detection of small HCCs [3]. The degree of hepatic parenchyma enhancement depends on a variety of factors, including contrast medium volume and concentration, rate and type of injection, scanning delay time, and body weight. These factors have been well analyzed and documented in previous studies [4–17]. The results of these studies implied that the use of at least 2.0 mL/kg of contrast medium (i.e., 100 mL for 50 kg body weight) with a standard iodine concentration (300 mg I/mL) would be necessary for optimal hepatic enhancement. In fact, in our clinical practice, we have often encountered insufficient liver enhancement during portal and late phase dynamic helical CT with a standard iodine concentration (300 mg I/mL) of contrast medium using prefilled syringes of a 100-mL dose with cirrhotic patients with body weights heavier

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2 mL/kg, 150# = 68 kg
68 x 2 = 136 mL
136 mL x 300 mg I/mL = 40.8 gm
136 mL x 370 mg I/mL = 50.3 gm!

than 60 kg. Here, we tried to examine the effect of the iodine concentration in the contrast medium on hepatic enhancement in cirrhotic patients who weighed more than 60 kg. Our aim was to evaluate the degree of hepatic enhancement and image quality in heavy patients with cirrhosis or chronic hepatitis who underwent multiphasic contrast-enhanced dynamic MDCT at least twice using standard (300 mg I/mL) and higher (370 mg I/mL) iodine concentrations in contrast medium during follow-up periods and to assess the usefulness of contrast medium in a high concentration. To eliminate the problem of interpatient variability, we compared standard and high iodine concentrations only in the same patients, who served as their own controls.

Materials and Methods

Patient Population

This study included twenty patients (19 men, one woman; age range, 40–70 years; mean age, 59.9 years) with cirrhosis or chronic hepatitis who underwent multiphasic contrast-enhanced dynamic MDCT at least twice between March 2000 and September 2002, using standard (300 mg I/mL) and higher (370 mg I/mL) iodine concentrations in the contrast medium. The time intervals between the two MDCT examinations were 49–192 days (mean, 113 days). Other inclusion criteria were that all patients were Japanese adults who weighed more than 60 kg and who underwent contrast-enhanced MDCT during the same period at our institution; that patients did not undergo hepatic resection or receive interventional procedures such as transcatheter arterial chemoembolization, percutaneous alcohol injection, or radiofrequency ablation during the two MDCT examinations; and that patients did not have a history of hypersensitivity to iodine contrast medium, renal failure, congestive heart failure, bronchial asthma, or hyperthyroidism. The range of patients' weight was 60–110 kg (mean, 72.3 kg). Weight gain or loss in the same patient between the MDCT examinations using the 300 mg I/mL contrast medium and the examination using the 370 mg I/mL contrast medium was less than five percent. The study was performed within the routine clinical standards of our hospital, and informed consent was obtained from all patients before their examinations.

MDCT Protocol

For the initial MDCT examination, all patients received 100 mL of IV contrast medium with a standard iodine concentration of 300 mg I/mL (Iopamiron 300 [iopamidol], Nihon Schering). At the second MDCT examination performed during the follow-up period, all patients received 100 mL of contrast medium with a higher iodine concentration of 370 mg I/mL (Iopamiron 370 [iopamidol], Nihon Schering) using the same MDCT protocol. This procedure allowed a comparison of the effect on liver enhancement of two different iodine concentrations of contrast medium in the same patient. As a result, the qualifying study population consisted of two groups of the same 20 patients each, using the standard iodine concentration of 300 mg I/mL (group A) and the higher iodine concentration of 370 mg I/mL (group B).

All examinations were performed with an MDCT scanner (Somatom Plus 4, Volume Zoom, Siemens Medical Solutions), with 2.5 × 4 beam collimation, 120 kVp, 250 mAs, 0.5-sec gantry rotation speed, 7.5 mm per rotation table speed, and 5-mm section thickness and interval. Before the examinations, patients were instructed to hold their breath to avoid motion artifacts. Unenhanced MDCT was performed first, starting from the top of the liver in the cephalocaudal direction before insertion of an IV catheter. Multiphasic (arterial, portal, and late phase) contrast-enhanced dynamic MDCT scans of the whole liver were performed next using the same scanning parameters. Contrast medium (warmed to body temperature) was administered with a power injector through a 22-gauge IV catheter into an antecubital vein. The rate of IV injection of the contrast medium was set at 3.0 mL/sec for all examinations. Multiphasic scanning was started with a 30-sec delay for the arterial phase, a 60-sec delay for the portal phase, and a 180-sec delay for the late phase from the time that the injection of the contrast medium began. SmartPrep (GE Healthcare) or timing bolus techniques were not used in our institution to shorten the total examination time.

Quantitative Analysis

After data acquisition, the attenuation values for the abdominal aorta, the hepatic parenchyma, and the portal vein were measured by one observer in a total of 40 examinations in 20 patients using a 1.0–2.0 cm^2 circular region-of-interest cursor on the unenhanced scans and on the three phases of the contrast-enhanced CT scans.

In the hepatic parenchyma, region-of-interest measurement was performed at three different sections of the upper, middle, and lower liver. In each section, regions of interest were measured at four areas: two separate areas of the right lobe and two separate areas of the left lobe. In the one patient who had undergone a hepatic left lobectomy, regions of interest were measured at four separate areas in the remaining right lobe, at three different sections. Thus, regions of interest were measured at 12 separate areas in all patients. The mean attenuation value was calculated by averaging the results of all measurements. An attempt was made to maintain a constant region of interest in the same patient and place the regions in approximately the same location on each section in the two examinations. Visible hepatic and portal vessels, bile ducts, possible hepatic lesions, and regions of posttreatment were excluded from region-of-interest measurements to reduce partial volume effects. In the abdominal aorta, attenuation values were measured at three different sections used for region-of-interest measurement in hepatic parenchyma, and the results were averaged. In the portal vein, attenuation values were measured at two areas at two different sections where the main portal vein was clearly seen, and the results were averaged.

For the evaluation of the change in attenuation of the liver, aorta, and portal vein, contrast enhancement values of these structures were calculated by subtracting attenuation values of the contrast-enhanced images obtained during the arterial, portal, and late phases from the corresponding baseline values on the unenhanced images. In each phase, contrast enhancement values between two examinations in the same patients were compared using a paired Student's *t* test. In the arterial phase, the liver-to-aorta contrast was also evaluated by calculating the absolute difference in the attenuation value between the aorta and the liver. In addition, the contrast enhancement value of the hepatic parenchyma during portal and late phases was classified in grades as follows; 3 = fine (mean increase, > 50 H), 2 = moderate (mean increase, 30–50 H), and 1 = insufficient (mean increase, < 30 H) to compare the adequacy of contrast enhancement between the two groups.

Visual Analysis

All the MDCT scans were reviewed by two experienced radiologists who had no knowledge of the iodine concentration in the contrast medium to qualitatively assess by consensus the degree of arterial, hepatic venous, portal venous, and hepatic parenchyma enhancement. All images were analyzed on a computer monitor. Two observers were asked to visually score the degree of vascular and hepatic enhancement with the use of a 4-point scale as follows: 4, excellent—very good contrast between hepatic parenchyma and hepatic vessels with clear visualization of peripheral vascular branches, and excellent overall image quality; 3, good—good contrast between hepatic parenchyma and hepatic vessels, and adequate image quality; 2, fair—insufficient contrast between hepatic parenchyma and hepatic vessels; 1, poor—little contrast between hepatic parenchyma and hepatic vessels. The visual analyses for the two groups were compared using the paired Student's *t* test.

Results

Quantitative Analysis

The results of quantitative analysis of hepatic parenchyma and aortic and portal venous enhancement values are summarized in Tables 1–3. The mean hepatic parenchyma enhancement values in group B was significantly greater ($p < 0.001$) than those in group A during the portal phase and the late phase, but the difference on the arterial phase images between the two groups was not significant. The mean differences in hepatic parenchyma enhancement values in individual persons between the two groups during the portal phase and the late phase were 7.7 H (range, 0.3–16.2 H) and 6.4 H (range, 0.3–11.5 H), respectively. The mean aortic enhancement value in group B was significantly higher ($p < 0.001$) than that in group A during the arterial phase and the portal phase. The mean differences in aortic enhancement values in individual persons

between the two groups during the arterial phase and the portal phase were 44.9 H (range, 14.8–64.0 H) and 22.4 H (range, 11.4–39.5 H), respectively. The mean portal venous enhancement values in group B were significantly higher ($p < 0.001$) than those in group A during the portal phase and the late phase. The mean differences in portal venous enhancement values in individual persons between the two groups during the portal phase and the late phase were 29.8 H (range, 5.9–76.2 H) and 14.7 H (range, 2.0–25.5 H), respectively. The mean aorta-to-liver contrast during the arterial phase in group B was significantly higher ($p < 0.001$) than that in group A.

The adequacy of contrast enhancement in hepatic parenchyma varied. In group B, grade 3 and grade 2 contrast enhancement during the portal phase were noted in four (20%) and 16 (80%) of the 20 patients, respectively. No patients with grade 1 contrast enhancement were found in group B. However, in group A, grade 3 and grade 2 contrast enhancement during the portal phase were noted in one (5%) and 15 (75%) of the 20 patients, respectively. Four patients (20%) with grade 1 contrast enhancement were in group A. During the late phase, grade 1 contrast enhancement was noted in 80% (16/20) of the patients in group A, but it was noted in only 45% (9/20) in group B.

Qualitative Analysis

The results of qualitative analysis of the hepatic and vascular enhancement in the two groups are summarized in Tables 4 and 5. The mean visual scores of hepatic parenchyma and vascular enhancement in group B were significantly higher than those in group A in arterial phase, $p < 0.018$; portal phase, $p < 0.0001$); and late phase, $p < 0.0001$). During the arterial phase and portal phase, 14 (70%) and 13 cases (65%) were assessed as grade 4 (excellent) in group B, but five (25%) and four cases (20%) were assessed as grade 4 in group A. During the late phase, six cases (30%) were assessed as grade 4 (excellent) in group B but only one case (5%) was assessed as grade 4 in group A.

Discussion

With the introduction of single helical or MDCT scanners, various studies have examined the effect of iodine dose and concentration, contrast medium volume, and injection parameters on aortic and hepatic parenchyma enhancement and lesion detectability [4–17]. However, previous studies that evaluated the effect of alterations of these factors made their comparisons between different patient groups. The potential for error in that approach lies in the interpatient variability in hepatic contrast enhancement values attributable to factors such as body weight or the presence of chronic liver diseases. Here, we compared the hepatic contrast enhancement between two examinations in the same patients.

Classic HCCs that develop in chronic hepatitis or cirrhosis are typically hypervascular and tend to be seen best during the arterial phase of contrast enhancement [18, 19]. However, some hypovascular HCCs such as well-differentiated HCCs and dysplastic nodules are more conspicuous or visible only on the

TABLE 1 Comparison of the Mean Contrast-Enhancement Values in Hepatic Parenchyma, Aorta, and Portal Vein Between Two Groups

Structure	Phase	Group A	Group B
Liver	Arterial	8.3 ± 2.5	9.4 ± 3.2
	Portal[a]	36.2 ± 7.3	43.8 ± 8.2
	Late[a]	27.6 ± 3.9	33.7 ± 7.0
Aorta	Arterial[a]	212.4 ± 29.8	257.3 ± 37.6
	Portal[a]	87.1 ± 11.6	109.5 ± 15.6
Portal vein	Portal[a]	101.0 ± 15.8	131.1 ± 19.4
	Late[a]	51.8 ± 8.6	66.5 ± 9.2

Note.—Data are mean ± standard deviation. Group A was administered contrast-enhancing medium in an iodine concentration of 300 mg I/mL, group B was administered contrast-enhancing medium in an iodine concentration of 370 mg I/mL.

[a] $p < 0.001$.

TABLE 2 Comparison of the Mean Aorta-to-Liver Contrast Between Two Groups

Phase	Group A	Group B
Arterial[a]	193 ± 32	236 ± 40
Portal[a]	40 ± 8	53 ± 12
Late[b]	14 ± 6	18 ± 9

Note.—Data are mean ± standard deviation. Group A was administered contrast-enhancing medium in an iodine concentration of 300 mg I/mL, group B was administered contrast-enhancing medium in an iodine concentration of 370 mg I/mL.

[a] $p < 0.001$.

[b] $p < 0.01$.

TABLE 3 Adequacy of Contrast Enhancement in Hepatic Parenchyma Between Two Groups

Enhancement	Portal Phase		Late Phase	
	Group A	Group B	Group A	Group B
> 50 H	1	4	0	0
30–50 H	15	16	4	11
< 30 H	4	0	16	9

Note.—Data indicate the number of patients. Group A was administered contrast-enhancing medium in an iodine concentration of 300 mg I/mL, group B was administered contrast-enhancing medium in an iodine concentration of 370 mg I/mL. $n = 20$ for all groups.

TABLE 4 Comparison of the Mean Visual Score Between Two Groups

Phase	Group A	Group B
Arterial[a]	3.10 ± 0.64	3.55 ± 0.75
Portal[a]	3.10 ± 0.55	3.55 ± 0.69
Late[a]	1.9 ± 0.79	2.8 ± 1.01

Note.—Data are mean ± standard deviation. Group A was administered contrast-enhancing medium in an iodine concentration of 300 mg I/mL, group B was administered contrast-enhancing medium in an iodine concentration of 370 mg I/mL.

[a] $p < 0.001$.

TABLE 5 Visual Scores of Hepatic Parenchymal and Vascular Enhancement Between Two Groups

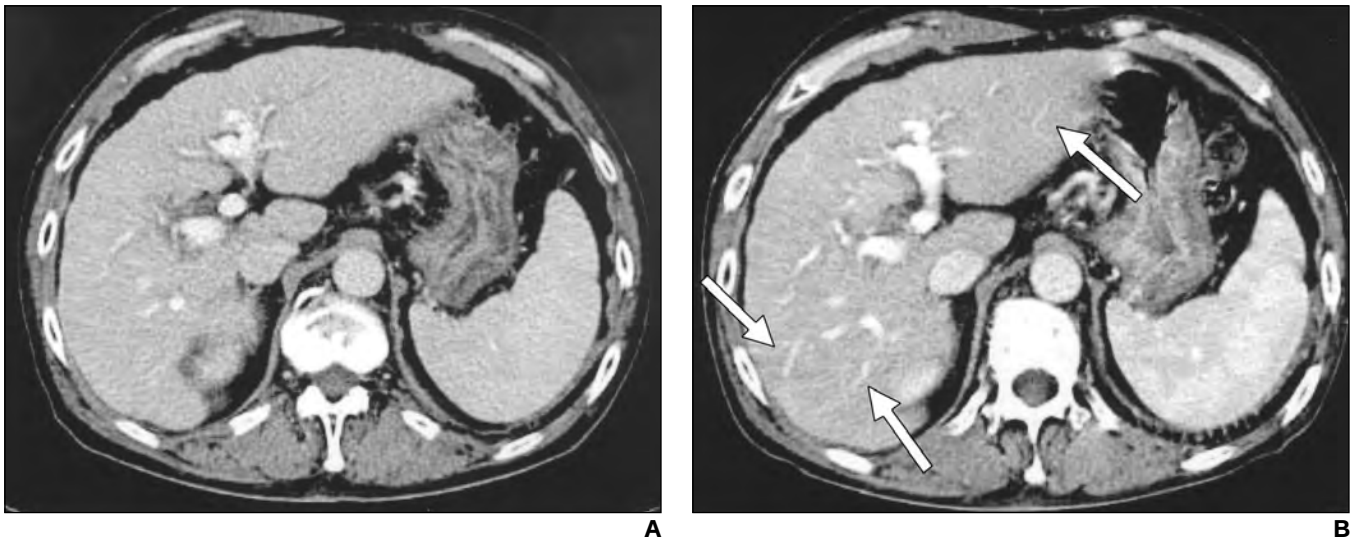
Score	Group A			Group B		
	Phase			Phase		
	Arterial	Portal	Late	Arterial	Portal	Late
4	5	4	1	14	13	6
3	12	14	2	3	5	6
2	3	2	11	3	2	6
1	0	0	6	0	0	2

Note.—Data indicate the number of patients. Group A was administered contrast-enhancing medium in an iodine concentration of 300 mg I/mL, group B was administered contrast-enhancing medium in an iodine concentration of 370 mg I/mL. $n = 20$ for both groups.

portal or late phase images [20, 21] (Figs. 1 and 2). Therefore, multiphasic (arterial, portal, and late phase) contrast-enhanced dynamic imaging is needed for screening CT examinations in patients with chronic hepatitis, cirrhosis, or suspected HCCs. A high degree of contrast between the hepatic parenchyma and lesions in every phase is necessary to obtain greater conspicuity of both hypervascular and hypovascular HCCs.

The desirable high lesion-to-liver contrast in hypovascular HCCs depends on a high degree of enhancement of the surrounding hepatic parenchyma during the portal and late phases. In our study, the mean hepatic parenchyma enhancement values in group B were significantly greater than those in group A during the portal phase and the late phase. In the qualitative analysis of the hepatic and vascular enhancement, 12 cases (60%) were assessed as grade 3 or 4 (good or excellent) in group B but only three cases (15%) were assessed as grade 3 or 4 in group A during the late phase. These results suggest that the injection of a contrast medium with a higher iodine concentration results in a significantly superior enhancement of hepatic parenchyma in the portal phase and the late phase in patients with cirrhosis and probably contributes to improved lesion detection and conspicuity of hypovascular HCCs in the portal phase and the late phase. The accuracy of detection must be evaluated in a future study.

The influence of the iodine concentration in contrast medium for hepatic enhancement in heavy patients with cirrhosis or chronic hepatitis may be great during the portal and late phases. Heiken et al. [13] reported that a hepatic peak enhancement of at least 50 H is desirable, judging from quantitative and qualitative analyses. Their results revealed that maximum hepatic enhancement values in the group of heavy patients were significantly lower than those in the group of lightweight patients using the same enhancement protocols. Vignaux et al. [22] reported that mean hepatic enhancement values in cirrhotic patients were significantly lower than those in patients without cirrhosis during the portal phase and found the plateau of hepatic enhancement in cirrhotic livers to occur during the late portal phase. These findings presumably reflect the decreased portal perfusion associated with cirrhosis. In general, only subtle contrast differences appear between hypovascular HCCs such as well-differentiated HCCs and the surrounding liver parenchyma during the portal and late phases. Therefore, a higher degree of hepatic enhancement is especially important at those times. In our analysis of the adequacy of contrast enhancement in hepatic parenchyma, insufficient contrast enhancement was noted in 80% (16/20) of the patients in group A but it was noted in only 45% (9/20) in group B during the late phase. This result suggests that the injection of a contrast medium with a standard iodine concentration leads to an increase in the number of suboptimal MDCT scans obtained during the late phase and may lead to overlooking the subtle contrast difference between hypovascular hepatocellular lesions and the surrounding liver parenchyma during the late phase in heavy patients with cirrhosis or chronic hepatitis.



A **B**

Fig. 1.—68-year-old man with cirrhosis.
A and **B**, Transverse dynamic CT scans obtained during portal phase using contrast medium concentrations of 300 mg I/mL (**A**) and 370 mg I/mL (**B**) show that intrahepatic portal branches (*arrows*) are visualized better in **B** than in **A**.

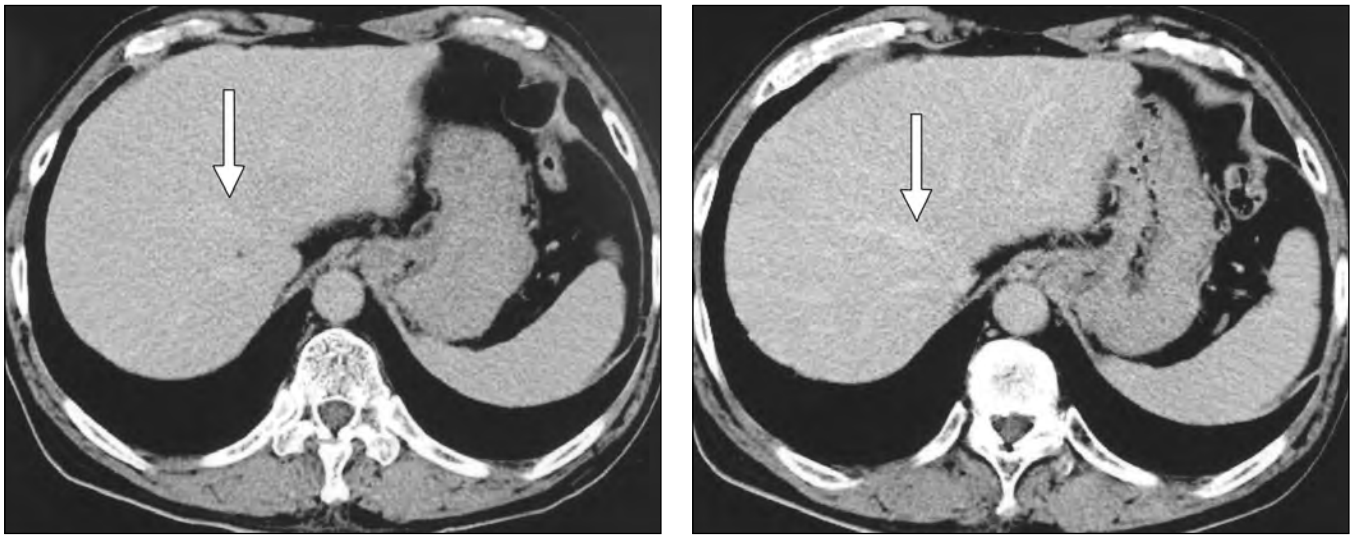


Fig. 2.—64-year-old man with cirrhosis.
A and **B**, Transverse dynamic CT scans obtained during late phase using contrast medium concentrations of 300 mg I/mL (**A**) and 370 mg I/mL (**B**) show that hepatic parenchyma enhancement (*arrows*) is greater in **B** than in **A**. Contrast enhancement values are 37 H and 27 H, respectively.

The better lesion-to-liver contrast in hypervascular HCCs is attributed to the maximum enhancement of the lesion with minimum enhancement of the surrounding hepatic parenchyma during the arterial phase. In this study, the mean aortic enhancement values with the higher iodine concentration were significantly higher than those with the standard iodine concentration during the arterial phase, suggesting the potential increase of the maximum enhancement of hypervascular HCCs fed by the hepatic artery. In addition, the hepatic parenchyma enhancement during the arterial phase between the two groups was not significantly different. As a result, the mean aorta-to-liver contrast during the arterial phase in group B was significantly higher than that in group A. Therefore, the conspicuity of hypervascular HCCs may not be increased to any substantial degree, although tumor conspicuity does not directly correspond to tumor detectability.

Yamashita et al. [14] evaluated the optimal dose of IV contrast medium with a standard iodine concentration (300 mg I/mL) for liver enhancement on helical CT as a function of patient weight. In a patient population with a mean body weight of 57.3 kg, these researchers recommended using at least 2.0 mL/kg of contrast medium with a standard iodine concentration for optimal liver enhancement during the portal phase. Their observation supports our finding that injection of a 100-mL dose of contrast medium with a standard iodine concentration was not sufficient for optimal liver enhancement during the portal and late phases in patients weighing more than 60 kg. Contrast enhancement values in our heaviest patient (110 kg) in the portal and the late phases were much lower than those in our lightest patient (60 kg), using the 100-mL dose (32.9 vs 49.2 H in portal phase, 21.9 vs 34.4 H in late phase). The difference may be important for treatment of patients with cirrhosis or chronic hepatitis or in Western populations of patients weighing more than 70 kg. The dose should be adjusted according to patient weight to achieve adequate contrast enhancement in most patients [14]. However, prefilled syringes (usually an empiric dose of 100 mL of contrast medium for Japanese adults) are more commonly used in the clinical field for convenience or sanitary reasons.

Our study has some potential limitations. First, in the patient population, generalized heterogeneity of hepatic parenchyma in advanced cirrhosis may have affected densitometric measurements. However, comparison was made between two examinations performed on the same patients with cirrhosis during the follow-up period. In addition, at least 11 attenuation measurements were averaged to correct heterogeneity, and unenhanced baseline values were taken into account to determine liver enhancement values.

Second, this study was based on two examinations on the same patients performed during follow-up periods, and time elapsed between them. Hepatic conditions such as severity of cirrhosis could have changed during the interim. Third, our patient population was relatively small, because our inclusion criteria limited participation to patients who weighed more than 60 kg who had cirrhosis or chronic hepatitis and who underwent multiphasic contrast-enhanced MDCT at least twice using a standard and a higher iodine concentration in the contrast medium. Further evaluation using a larger patient population is needed.

Finally, although we used a standardized CT protocol for the contrast medium dose, injection rate and scanning delay time for all patients were based on those used in previously published studies [14, 22] and clinical availability (e.g., the use of prefilled syringes with a 100-mL dose) and may not have been optimal. Also, a timing bolus technique was not applied for all patients. However, a comparison was performed between the same groups of patients without cardiovascular diseases, resulting in little influence on interpatient variations in liver and vascular enhancement.

In conclusion, in patients with chronic liver diseases, a higher iodine concentration (370 mg I/mL) in the contrast medium improves contrast enhancement of liver parenchyma in portal and late phase images, the

overall image quality, and diagnostic accuracy for liver diseases in multiphasic contrast-enhanced dynamic MDCT.

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