

This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 3.0 License ([www.karger.com/OA-license](http://www.karger.com/OA-license)), applicable to the online version of the article only. Distribution for non-commercial purposes only.

# Drinking Status of Heavy Drinkers Detected by Arrival Time Parametric Imaging Using Sonazoid-Enhanced Ultrasonography: Study of Two Cases

Noritaka Wakui<sup>a</sup> Ryuji Takayama<sup>a</sup> Takahiko Mimura<sup>a</sup>  
Naohisa Kamiyama<sup>c</sup> Kenichi Maruyama<sup>b</sup> Yasukiyo Sumino<sup>a</sup>

<sup>a</sup>Division of Gastroenterology and Hepatology and <sup>b</sup>Division of Clinical Functional Physiology, Toho University Omori Medical Center, Tokyo, and <sup>c</sup>The Ultrasound Systems, Development Department, Toshiba Medical Systems Corporation, Otawara, Japan

## Key Words

Alcoholic liver disease · Contrast-enhanced ultrasonography · Arrival time parametric imaging · Sonazoid · Liver

## Abstract

Chronic heavy consumption of alcohol is associated with increased risks of developing liver cirrhosis, hepatocellular carcinoma, and esophageal varices. Cessation of alcohol consumption is the most important requirement in treating these diseases. However, judging whether patients have actually maintained abstinence from alcohol requires reliance on their reports, which vary substantially across individuals using the test methods currently available. Arrival time parametric imaging (At-PI) using Sonazoid-enhanced ultrasonography is regarded as a useful approach for assessing the progression of lesions that have developed in liver parenchyma. In this study, we report two cases for whom this approach was successfully applied to indicate the drinking status of a heavy drinker. At-PI enables approximate and objective assessment of the drinking status of patients, independent of their reports; therefore, it is a promising method for providing information about drinking status.

## Introduction

In Japan, alcoholic drinks have been consumed during ceremonies since ancient times and have become popular as grocery items among the general public. However, chronic heavy consumption of alcohol can induce alcoholic liver disease that may progress to liver

cirrhosis, which in turn leads to increased incidence of esophageal varices and hepatocellular carcinoma [1–3]. Prognosis of alcoholic liver cirrhosis induced by excessive consumption of alcohol is poor, and the 5-year survival rate was reported to be 40.5% [4]. On the other hand, it is known that successful cessation of alcohol consumption markedly ameliorates liver cirrhosis [5, 6]. Therefore, patient commitment to remaining abstinent from alcohol is the ultimate determinant of prognosis for this disease. Moreover, reversibility of hepatic fibrosis has been proven histologically [7], and long-term abstinence from alcohol has been reported to reduce pre-existing fibrosis, which consequently decreases portal pressure, leading to a possible amelioration of esophageal varices [8].

During medical consultations, however, patients often deny or conceal the fact that they are regularly consuming alcohol, and the information they provide regarding their alcohol consumption habits tends to be inaccurate. To overcome this problem, the ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT ratio), gamma-glutamyl transpeptidase ( $\gamma$ -GTP) activity, and the level of IgA were suggested as indicators of drinking status since they play a role in diagnosing alcoholic liver cirrhosis [9–13]. However, measuring these indicators does not provide conclusive evidence of drinking status because the magnitude of changes in these measurements varies considerably across individuals [11–13]. This means that accurate understanding of patients' drinking status is still dependent on their reports. Therefore, a different approach that enables objective assessment of drinking status will be of great benefit in daily clinical practice.

Arrival time parametric imaging (At-PI) using Sonazoid-enhanced ultrasonography is regarded as a useful approach for assessing the progression of lesions that have developed in liver parenchyma. In this study, we employed this approach to assess the drinking status of two heavy drinkers. We report interesting findings when comparing patients' drinking status as indicated by At-PI-based laboratory test results against their reports.

## Case Report

### *Liver Parenchyma Blood Flow Imaging*

A Toshiba SSA-790 system (Aplio XG; Toshiba Medical Systems, Otawara, Japan) with a 3.75 MHz convex array probe (PVT-375BT; Toshiba Medical Systems) was used for blood flow imaging. The system was operated at a mechanical index of 0.22–0.29 and a frame rate of 15–18 frames/s, and right intercostal images were acquired to view the liver and kidney on the same screen simultaneously. The focal depth was adjusted within a range of 6–8 cm depending on the thickness of the kidney. Then, the recommended amount (0.015 ml/kg) of Sonazoid (perfluorobutane; GE Healthcare, Oslo, Norway) was injected into the antecubital vein. Imaging was started immediately after injection for a period of approximately 40 s, and the acquired images were stored as raw data in the system hardware.

### *At-PI*

To study the kinetics of the ultrasound signals, arrival time parametric images of the liver parenchyma were constructed from ultrasound raw data using a software program (At-PI; Toshiba Medical Systems) that interfaced with the ultrasound system. Briefly, the stored video was started after selecting the region of interest within the kidney parenchyma on a still image. Construction of an arrival time parametric image was started automatically when the signal intensity exceeded the set level in 80% of the region of interest. The time interval from the start of the construction (time 0) to the appearance

of contrast (arrival time) in individual pixels of the liver parenchyma imaging agent was depicted using multiple colors for different arrival times as follows: red 0–1 s; orange 1–2 s; yellow 2–3 s; light green 3–4 s; dark green 4–5 s; light blue 5–6 s; dark blue 6 s or longer ([fig. 1](#)). This study was approved by the institutional ethics committee, and informed consent was obtained from the patients.

### Case 1

Case 1 was a 60-year-old male who managed a bar and had been drinking heavily for 20 years. He consumed 2 mid-sized glasses of beer and 10 glasses of shochu liquor mixed with warm water on a daily basis (effective ethanol consumption: 200 g/day). After liver dysfunction was indicated by a blood test performed as part of a health checkup, he visited Toho University Omori Medical Center in April 2009. Laboratory findings on admission were: ammonia (NH<sub>3</sub>) 78 µg/dl; albumin (Alb) 2.8 g/dl; total bilirubin (T-bil) 1.4 mg/dl; direct bilirubin (D-bil) 0.7 mg/dl; AST 102 IU/l; ALT 45 IU/l; lactate dehydrogenase (LDH) 329 IU/l; alkaline phosphatase (ALP) 331 IU/l; γ-GTP 266 IU/l; cholinesterase (ChE) 96 IU/l; platelets (Plt) 40 × 10<sup>4</sup>/µl; prothrombin time (PT) 45%; antibodies to hepatitis C virus (HCVAb) negative; hepatitis B surface antigen (HBsAg) negative; antibodies to hepatitis B surface antigen (HBsAb) negative. These findings indicated elevation of transaminase levels with AST dominance and deterioration of liver function.

The patient tried to remain abstinent from alcohol and follow-up laboratory tests showed that levels of AST, ALT, γ-GTP, and PT had improved to 24, 27, and 136 IU/l and 71%, respectively, in December 2009, and further to 21, 21, and 104 IU/l and 75%, respectively, in July 2010 ([table 1](#)). At-PI results in April 2009, December 2009, and July 2010 are shown in [figure 2](#), [figure 3](#) and [figure 4](#), respectively. Red, indicative of early arrival time, was the dominant color in the entire region of the arrival time parametric image of the liver taken in April 2009, while blue, indicative of late arrival time, was more dominant in more recent images. In other words, it was suggested that blood flow to the liver had slowed during the follow-up period.

### Case 2

Case 2 was a 51-year-old patient with liver damage who was referred to Toho University Omori Medical Center by a local physician in March 2010. He had been consuming 900 ml of shochu liquor on a daily basis for 30 years (effective ethanol consumption: 225 g/day). Laboratory findings on admission were: NH<sub>3</sub> 24 µg/dl; Alb 1.8 g/dl; T-bil 2.4 mg/dl; D-bil 1.4 mg/dl; AST 53 IU/l; ALT 13 IU/l; LDH 219 IU/l; ALP 922 IU/l; γ-GTP 658 IU/l; ChE 80 IU/l; Plt 41 × 10<sup>4</sup>/µl; PT 33%; HCVAb negative; HBsAg negative; HBsAb negative. These findings indicated elevation of transaminase levels with AST dominance and deterioration of liver function. Red, indicative of early arrival time, was the dominant color in the entire region of the arrival time parametric image of the liver constructed from Sonazoid-enhanced ultrasound results ([fig. 5](#)).

The first follow-up examination was performed in May 2010. The patient reported that he had remained abstinent from alcohol and laboratory tests showed that levels of AST, ALT, γ-GTP, and PT had improved to 21, 5, and 157 IU/l and 46%, respectively ([table 2](#)). At-PI showed that yellow, indicating an arrival time of 2–3 s, had increased ([fig. 6](#)), suggesting that blood flow into the liver had slowed. The second follow-up examination was performed in July 2010, and the patient reported that he had not consumed alcohol since the previous examination. Laboratory tests showed an increase in PT (63%), suggesting liver function improvement, while levels of AST, ALT, and γ-GTP were not improved, but elevated to 53, 13, and 408 IU/l, respectively ([table 2](#)). The arrival time parametric image of the entire liver had reverted to a red-dominated image, suggesting that the blood flow into the liver had improved ([fig. 7](#)). The patient was re-questioned about his recent drinking status while presenting the At-PI results. His answers revealed that he had resumed drinking 1 month earlier and has been consuming 900 ml of shochu liquor on a daily basis (effective ethanol consumption: 225 g/day).

## Discussion

The liver receives a dual blood supply from the hepatic portal vein and hepatic arteries, both of which drain blood into the hepatic vein via the liver sinusoids. It is understood that both the former and latter deliver a crucial supply of blood to the hepatocytes and cholangiocytes, respectively. In healthy individuals, the hepatic portal vein and hepatic arteries supply approximately 80 and 20% of liver blood, respectively [14]. In patients with viral hepatitis, this balance is altered toward arterial supply in line with the progression of chronic hepatitis to hepatic cirrhosis, since necrosis and loss of hepatocytes occur, which subsequently causes changes such as regeneration of liver tissue and fibrosis [14–17].

On the other hand, in patients with alcoholic liver disease induced by heavy drinking, elevation of portal venous pressure is seen even though the disease has not yet progressed to hepatic cirrhosis. Thickening of the central venous wall has been suggested as a potential reason for this pressure increase [18], and a mechanism involving the direct action of alcohol on collagen metabolism, independent of fibrosis caused by necrosis and inflammation, was proposed [19]. Changes associated with acute alcoholic hepatitis appear reversible. Necrosis and inflammatory cell infiltration induced by a large consumption of alcohol were reduced by the end of the fourth week of abstinence from alcohol, and deposition of basement membrane components including type IV collagen and laminin in the sinusoids was reduced, while histological findings characteristic of alcoholic hepatitis, such as expression of factor VIII-related antigen in sinusoidal endothelial cells, disappeared approximately 10 weeks after cessation of alcohol consumption [20]. Taken together, continuous heavy drinking elevates portal venous pressure which disturbs the normal balance of the dual blood supply to the liver (portal venous flow:arterial flow = 8:2). In response, the arterial flow increases to compensate for the decreased portal venous flow, and consequently, the blood supply balance shifts toward arterial domination [15]. Furthermore, this altered balance can be reverted to portal venous domination by abstaining from drinking.

At-PI is an ultrasound image analysis tool that monitors the intensity of ultrasound signals over time and presents color-coded images converted from sequential raw data. The At-PI-based approach used in this study is based on the relative time taken for blood flow to arrive at the liver compared to that of the kidney. The kidney receives blood from only the renal arteries, while the liver receives blood from both the hepatic portal vein and hepatic arteries; this difference is the reason why time 0 of At-PI of the liver is set as the arrival time of a contrast agent into the kidney. Chronic heavy drinking alters the hepatic blood supply balance from portal venous flow to arterial flow, and this imbalance can be predicted by studying the interval between the arrival time of the blood flow to the kidney (via the arterial route) and that to the liver. In other words, when the interval becomes shorter, the dominant source of the ultrasound signals in the liver is thought to arise more from the arterial flow than from the portal venous flow. Therefore, this approach enables objective assessment of blood supply balance between the hepatic portal venous flow and arterial flow.

When studying the balance of the dual blood supply system of the liver, the interval between the arrival time of blood flow to the liver parenchyma via the portal vein and that via the arteries is another important factor because it indicates roughly the dominant supply route: the hepatic portal venous route or arterial route. In healthy individuals, the

arrival time interval is reported to be approximately 5–6 s [21]. With respect to the color code used in this study, arrival time parametric color images dominated by light and dark blue (arrival time interval of 5 s or longer) can be interpreted as indicating that the portal vein is the main route of blood flow to the liver parenchyma. Light and dark blue-colored liver images also suggest the possibility that the blood supply condition is similar to that of a healthy individual; in other words, patients have successfully remained abstinent from alcohol or reduced consumption of alcohol. Conversely, red-dominated liver images suggest the possibility that the patient continued drinking heavily.

When the results of case 1 were assessed according to the above-mentioned color-based system, the initial red-dominated image, taken at the time the patient was drinking heavily and indicative of the dominance of arterial blood supply to the liver parenchyma, changed to a blue-dominated image after cessation of alcohol consumption, suggesting that the slow velocity flow, namely the hepatic portal venous flow, became the dominant supply to the liver. Similarly, the initial red-dominated image of case 2 became more yellow after cessation of alcohol consumption. However, this sign of improvement reverted to the previous state, and most of the arrival time parametric image became red upon reintroduction of alcohol.

The results revealed that At-PI of liver parenchyma provides easy-to-understand color-coded visual information regarding the balance between hepatic arterial flow and portal venous flow. Moreover, because this approach enables objective assessment of the drinking status of patients on the basis of one final still image, it provided convincing evidence to the patient in case 2, whose laboratory test results had been contradicted by his self-reported status of alcohol consumption, to abstain from consuming alcohol. However, this approach does not provide quantitative information on the amount of alcohol consumed, and its application is currently limited to comparative assessment between two examinations performed on different dates, whereby only an increase or decrease in alcohol consumption is indicated. Development of a new approach enabling quantitative assessment of alcohol consumption is anticipated in the future. Nevertheless, considering that At-PI offers objective data indicating approximate alcohol consumption status, independent of the reports made by patients, it is suggested that arrival time parametric image will become a powerful indicator of alcohol consumption.

**Table 1.** Case 1

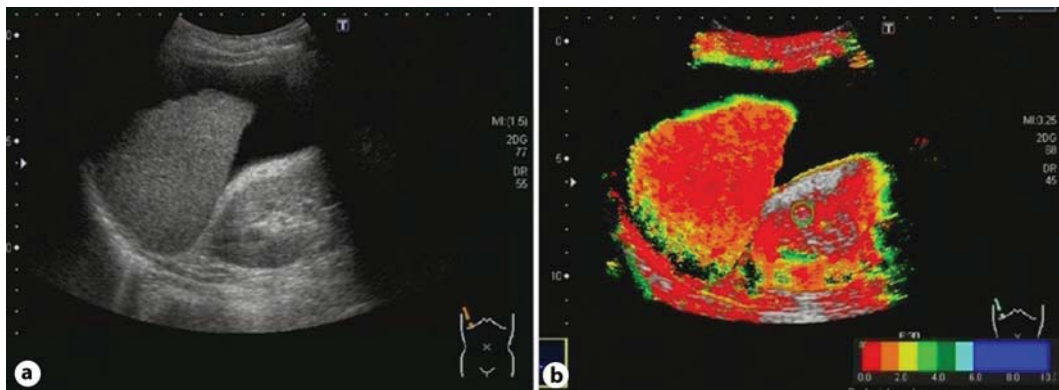
	April 2009	December 2009	July 2010
NH <sub>3</sub> , µg/dl	78	57	55
Alb, g/dl	2.8	3.7	3.9
T-bil, mg/dl	1.4	0.8	0.7
D-bil, mg/dl	0.7	0.2	0.1
AST, IU/l	102	24	21
ALT, IU/l	45	27	21
LDH, IU/l	329	183	172
ALP, IU/l	331	462	390
γ-GTP, IU/l	266	136	104
ChE, IU/l	96	249	259
Plt, ×10 <sup>4</sup> /µl	40	17.8	18.8
PT, %	45	71	75
HCVAb	(–)		
HBsAg	(–)		
HBsAb	(–)		

**Table 2.** Case 2

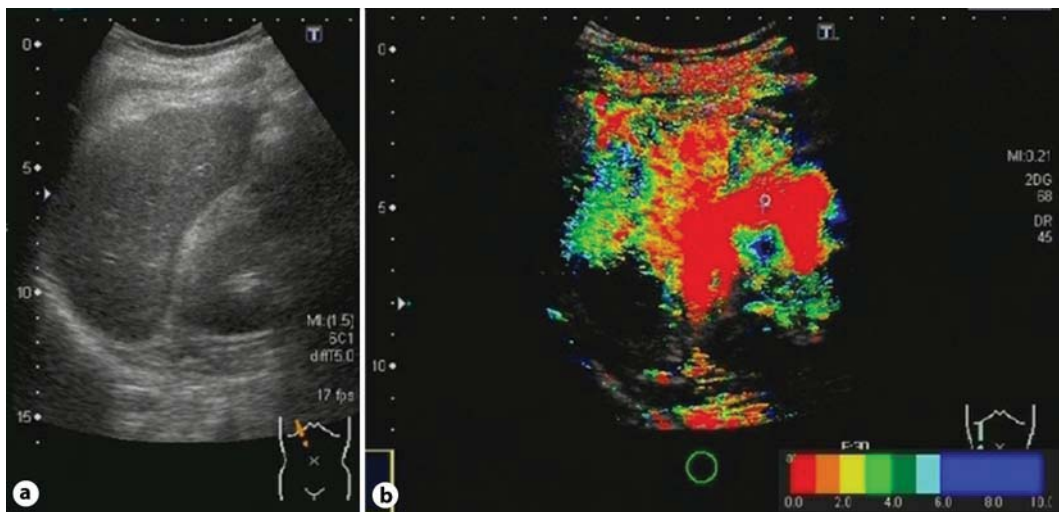
	March 2010	May 2010	July 2010
NH <sub>3</sub> , µg/dl	24	–	–
Alb, g/dl	1.8	3.4	4.3
T-bil, mg/dl	2.4	1.7	2.9
D-bil, mg/dl	1.4	0.7	1.5
AST, IU/l	53	21	53
ALT, IU/l	13	5	13
LDH, IU/l	219	140	199
ALP, IU/l	922	258	359
γ-GTP, IU/l	658	157	408
ChE, IU/l	80	194	27
Plt, ×10 <sup>4</sup> /µl	41	21	10.5
PT, %	33	46	63
HCVAb	(–)		
HBsAg	(–)		
HBsAb	(–)		



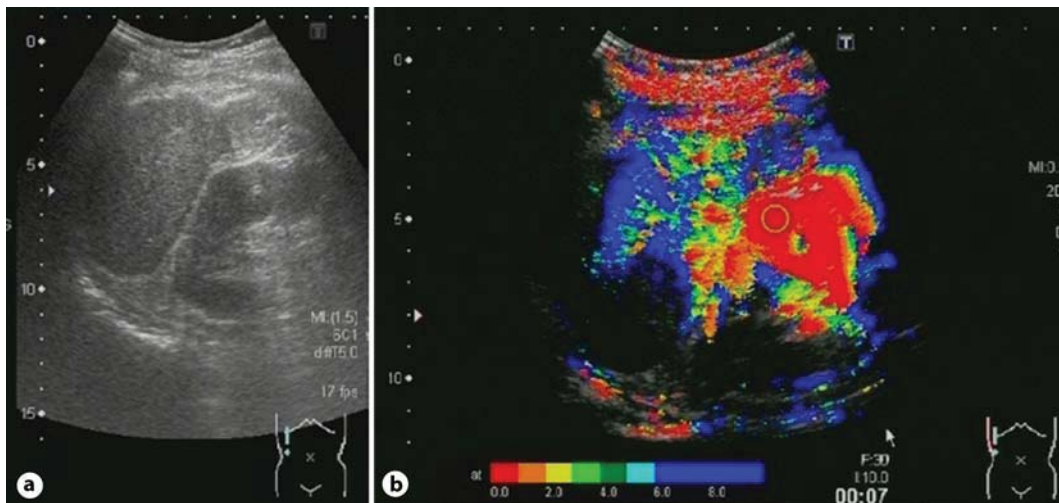
**Fig. 1.** Colors used in arrival time parametric images and the corresponding arrival times for the contrast agent to arrive in the liver are shown as follows: red 0–1 s; orange 1–2 s; yellow 2–3 s; light green 3–4 s; dark green 4–5 s; light blue 5–6 s; dark blue 6 s or longer.



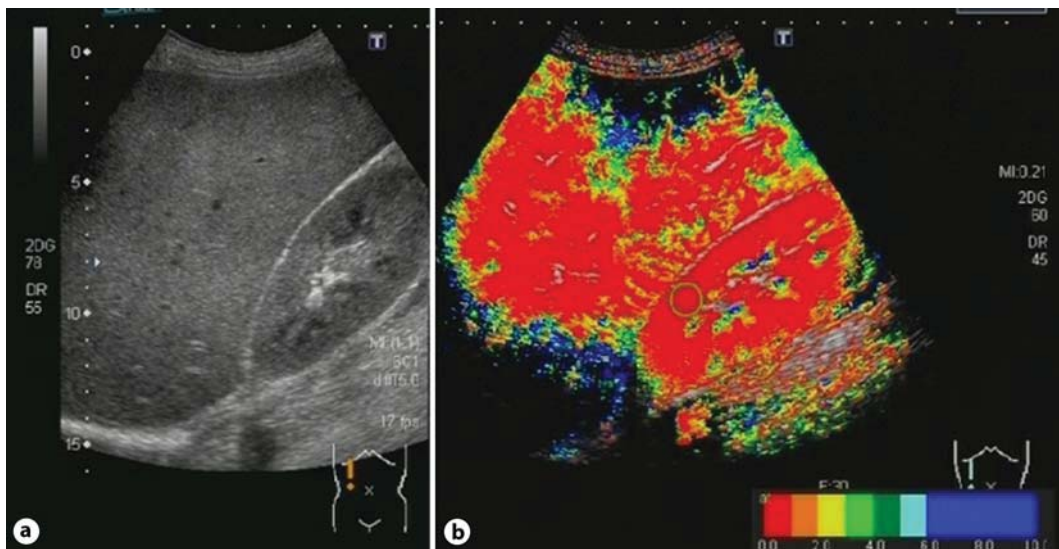
**Fig. 2.** Ultrasound images of case 1 taken in April 2009. **a** B-mode ultrasound image. **b** Arrival time parametric image. Red is dominant in the entire area of the arrival time parametric image of the liver.



**Fig. 3.** Ultrasound images of case 1 taken in December 2009. **a** B-mode ultrasound image. **b** Arrival time parametric image. The red-colored region decreased, while light and dark green-colored regions increased in the entire area of the arrival time parametric image of the liver.

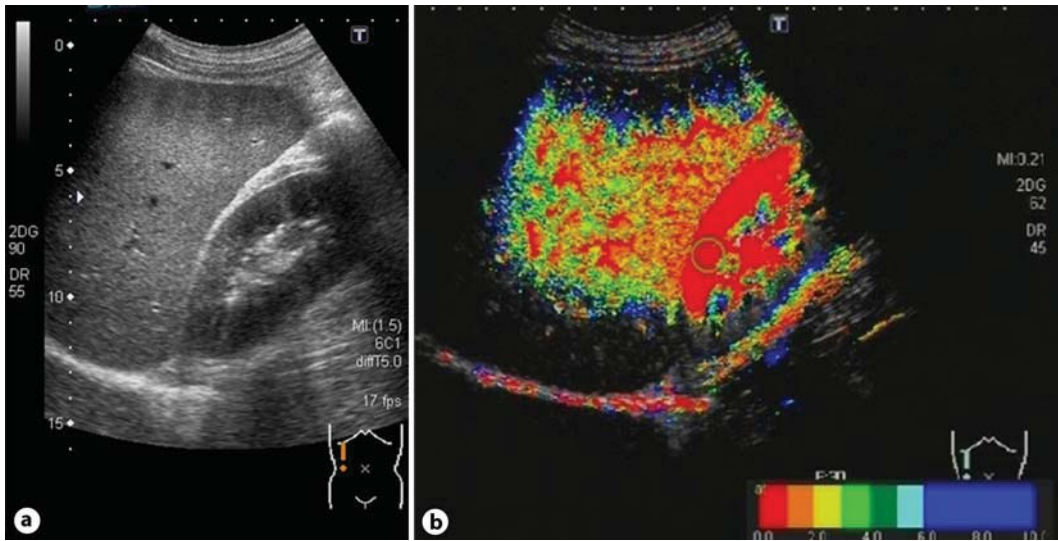


**Fig. 4.** Ultrasound images of case 1 taken in July 2010. **a** B-mode ultrasound image. **b** Arrival time parametric image. Blue, indicative of late arrival, dominated the entire area of the arrival time parametric image of the liver.

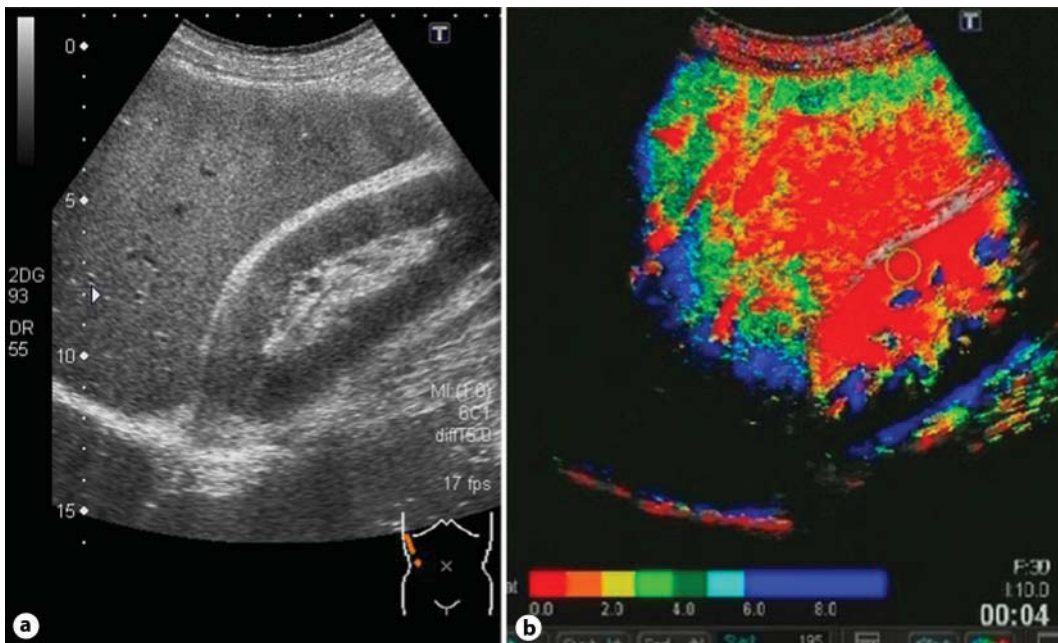


**Fig. 5.** Ultrasound images of case 2 taken in March 2010. **a** B-mode ultrasound image. **b** Arrival time parametric image. Red, indicative of early arrival, dominated the entire area of the arrival time parametric image of the liver.





**Fig. 6.** Ultrasound images of case 2 taken in May 2010. **a** B-mode ultrasound image. **b** Arrival time parametric image. The red-colored region decreased, while yellow- and light green-colored regions increased in the entire area of the arrival time parametric image of the liver.



**Fig. 7.** Ultrasound images of case 2 taken in July 2010. **a** B-mode ultrasound image. **b** Arrival time parametric image. The ratio of the red-colored region, indicative of early arrival, increased for a second time in the entire area of the arrival time parametric image of the liver.

## References

- 1 Tsutsumi M, Ishizaki M, Takada A: Relative risk for the development of hepatocellular carcinoma in alcoholic patients with cirrhosis: A multiple logistic regression coefficient analysis. *Alcohol Clin Exp Res* 1996;20:758–762.
- 2 Adachi M, Brenner DA: Clinical syndromes of alcoholic liver disease. *Dig Dis* 2005;23:255–263.
- 3 Tilg H, Day CP: Management strategies in alcoholic liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:24–34.
- 4 Powell WJ, Klatskin G: Duration of survival in patients with Laennec's cirrhosis. *Am J Med* 1968;44:406–420.
- 5 Merkel C, Marchesini G, Fabbri A, et al: The course of galactose elimination capacity in patients with alcoholic cirrhosis: possible use as a surrogate marker for death. *Hepatology* 1996;24:820–823.
- 6 Yokoyama A, Matsushita S, Ishii H, et al: The impact of diabetes mellitus on the prognosis of alcoholics. *Alcohol* 1994;29:181–186.
- 7 Nakano M: Histological changes of alcoholic fibrosis after abstinence in baboon (in Japanese). *Alcohol Biomed Res* 1996;16:137–140.
- 8 Fujii M, Nakano S, Hachiya A: Abstinent efficacy estimated by hepatic function and portal venous pressure in liver cirrhosis (in Japanese). *JJPH* 2001;7:213–217.
- 9 Cohen JA, Kaplan MM: The SGOT/SGPT ratio – an indicator of alcoholic liver disease. *Dig Dis Sci* 1979;24:835–838.
- 10 Matloff DS, Selinger MJ, Kaplan MM: Hepatic transaminase activity in alcoholic liver disease. *Gastroenterology* 1980;78:1389–1392.
- 11 Ishii H, Asuraoka S, Shigeta Y, et al: Hepatic and intestinal gamma-glutamyltranspeptidase activity: its activation by chronic ethanol administration. *Life Sci* 1978;23:1393–1397.
- 12 Morgan MY, Ross MG, Ng CM, et al: HLA-B8, immunoglobulins, and antibody responses in alcohol related liver disease. *J Clin Pathol* 1980;33:488–492.
- 13 Irie M, Suzuki N, Sohda T, et al: Hepatic expression of gamma-glutamyl transpeptidase in the human liver of patients with alcoholic liver disease. *Hepatol Res* 2007;37:966–973.
- 14 Kleber G, Steudel N, Behrmann C, et al: Hepatic arterial flow volume and reserve in patients with cirrhosis: use of intra-arterial Doppler and adenosine infusion. *Gastroenterology* 1999;116:906–914.
- 15 Rocheleau B, Ethier C, Houle R, et al: Hepatic artery buffer response following left portal vein ligation: its role in liver tissue homeostasis. *Am J Physiol* 1999;277:G1000–G1007.
- 16 Leen E, Goldberg JA, Anderson JR, et al: Hepatic perfusion changes in patients with liver metastases: comparison with those patients with cirrhosis. *Gut* 1993;34:554–557.
- 17 Lauth WW: Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response. *Am J Physiol* 1985;249:G549–G556.
- 18 Edmondson HA, Peters RL, Reynolds TB, et al: Sclerosing hyaline necrosis of the liver in the chronic alcoholic: A recognizable clinical syndrome. *Ann Intern Med* 1963;59:646–673.
- 19 Popper H, Lieber CS: Die alkoholische Zirrhose folgt nicht notwendigerweise der Alkoholhepatitis. *Internist (Berl)* 1979;20:176–178.
- 20 Urashima S, Tsutsumi M, Nakase K, et al: Studies on capillarization of the hepatic sinusoids in alcoholic liver disease. *Alcohol Alcohol Suppl* 1993;1B:77–84.
- 21 Iijima H, Sasaki S, Moriyasu F, et al: Dynamic US contrast study of the liver: Vascular and delayed parenchymal phase. *Hepatol Res* 2007;37:27–34.