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COMPARISON OF THE HEMODYNAMICS BETWEEN PATIENTS WITH ALCOHOLIC OR HCV-RELATED CIRRHOSIS

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ABSTRACT

BACKGROUND: Hyperdynamic circulation, which is characterized by increased cardiac output (CO), normal or low arterial blood pressure (BP), and decreased systemic vascular resistance (SVR), occurs in patients with liver cirrhosis (LC). However, differences of hemodynamics between patients with alcoholic LC (ALC) and viral LC are not well understood. **AIM:** The aim of the present study was to compare hemodynamics between patients with alcoholic LC and patients with HCV-related LC (CLC). **METHODS:** Eighteen healthy Japanese volunteers (HV), 10 patients with chronic hepatitis (CH), 46 patients with CLC, and 22 ALC patients with ALC were included in the study. The CLC group was divided into two subgroups (34 non-ascites and 12 ascites patients), as was the ALC group (11 non-ascites and 11 ascites patients). The CO, portal blood flow (PBF), and hepatic congestion index (HCI) were measured by ultrasound. **RESULTS:** The CO of the CLC and the ALC groups was higher than that of the HV group, while the SVR of the CLC and ALC groups was lower than that of the HV group. These changes were more marked in the ALC group. The HCI of the ascitic ALC subgroup was higher than that of the HV group. PBF did not differ among the CLC, ALC and HV groups. **CONCLUSIONS:** Progression of liver diseases such as ALC or CLC leads to a hyperdynamic circulation. The decrease of SVR was more marked in ALC patients than that CLC patients and an increase of the HCI was only found in ALC patients with ascites.

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I. INTRODUCTION

Systemic hemodynamics are characterized by primary peripheral arterial dilation, and a secondary increase of cardiac output prior to the development of ascites in experimental cirrhosis models, and compensated cirrhosis in humans (1-3). Progression of various liver diseases is accompanied by histologic changes of the hepatic parenchyma, such as inflammation, fibrosis, and necrosis, as well as by systemic hemodynamic changes. Liver cirrhosis (LC) is complicated by a hyperdynamic circulation that is characterized by generalized arterial dilatation with increased cardiac output (CO), normal or low arterial blood pressure (BP), and decreased systemic vascular resistance (SVR). The vasodilatation is caused by mechanisms such as a decrease of responsiveness to vasoconstrictors and increased responsiveness to vasodilators. The onset of hyperdynamic circulation is generally considered to be independent of the etiology of the liver disease (4,5), but few studies have specifically been performed to compare hemodynamic changes between patients with alcoholic LC (ALC) and those with viral LC. Duplex Doppler ultrasound is a safe and reproducible technique for evaluating hemodynamics in patients with cirrhosis and ascites. Rivolta et al. have reported that LC patients show decreased portal blood flow and an increased hepatic congestion index (HCI) on duplex Doppler examination, and that only the HCI is correlated with the severity of ascites, indicating that it is also a reliable measure of the severity of portal hypertension in patients with ascites (6). However, these studies did not assess differences between LC patients with or without ascites stratified according to the etiology of cirrhosis.

The present study was therefore retrospectively designed to compare

hemodynamics between patients with ALC and those with HCV-related LC (CLC), as well as to compare Doppler parameters in relation to the presence or absence of ascites in the ALC and CLC groups.

II. METHODS

Patients

In a 6-year period from 2000 to 2005, 18 healthy Japanese volunteers (HV group: 11 men and 7 women), 10 Japanese patients with chronic hepatitis due to hepatitis C virus infection (CH group: 7 men and 3 women), 46 Japanese patients with HCV-related LC (CLC group: 29 men and 17 women), and 22 Japanese patients with alcoholic LC (ALC group: 22 men) were investigated. The CLC group was divided into two subgroups, which were 34 patients without ascites (20 men and 14 women) and 12 patients with ascites (9 men and 3 women). The ALC group was also divided into two subgroups, which were 11 patients without ascites (11 men) and 11 patients with ascites (11 men). The Child-Pugh class was A for 24 patients, B for eight patients, and C for two patients among 34 patients in the non-ascitic CLC group, while the respective numbers were 0, 10, and 2 among the 12 patients in the ascitic CLC group. The Child-Pugh class was A for five and B for six patients among the 11 patients in the non-ascitic ALC group, while there were 7 patients in class B and 4 patients in class C among the 11 patients in the ascitic ALC group (Table 1). Diagnosis of liver disease was based on the clinical course, biochemical profile, imaging findings on abdominal ultrasound and computed tomography, and liver biopsy findings. The CH group had stage 1 or 2 disease according to Desment's fibrosis score. Patients with hypertension,

renal failure, cancer, or a portacaval shunt were excluded from this study. Written informed consent was obtained from all of the patients.

Measurement of echo-Doppler parameters

A Toshiba Sonolayer SSA-270A (Toshiba, Tokyo, Japan) for color Doppler sonography and a 3.75 MHz sector electronic probe were used. After limitation of salt intake to 6 g/day for a week, we measured the CO, portal blood flow (PBF) volume, mean PBF velocity, portal vein cross-sectional area, and hepatic congestion index (HCI) by ultrasound. SVR was calculated from the mean BP and CO (mean BP*CO/80). PBF volume was calculated as the time-averaged maximum velocity multiplied by 0.57, assuming that the portal velocity profile was parabolic, as reported previously. PBF was calculated as the portal vein cross-sectional area assuming a circular shape of the portal vein section multiplied by the mean PBF velocity (7, 8). HCI was calculated in accordance with the method of Moriyasu et al. (9) as the portal vein cross-sectional area divided by the mean PBF velocity.

The CO and SVR were normalized for body surface area because there were differences of sex and physique among the subjects.

Measurement of the hepatic venous pressure gradient

Portal pressure was determined from the hepatic venous pressure gradient (HVPG), which was obtained by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. Hepatic vein catheterization was perfomed percutaneously via the jugular vein and pressure was recorded in both the wedged state

(occluded) and the free state. Wedging of the catheter was confirmed by injection of contrast medium after recording the pressure. The wedged hepatic vein pressure was recorded in the right lobe three times in each patients and the mean of these three measurements was calculated. Hepatic vein catheterization and measurement of hepatic vein pressure were performed by the same operator in all patients (10).

Statistical analysis

Dunnett's test was used to compare the characteristics of the subjects among the groups. Results are expressed as the mean $\pm$ SD. A probability value of less than 0.05 was considered to indicate statistical significance.

III. RESULTS

Hemodynamic changes related to progression of liver disease

To clarify whether the progression of liver disease induced changes of the circulation and whether there were any differences of hemodynamics in relation to the etiology of LC, we compared the mean BP, CO, and SVR among each group. The mean BP of the CH group (86.9 ± 7 mmHg), the CLC group (91.9 ± 9 mmHg), and the ALC group (86.6 ± 8 mmHg) did not differ from that of the HV group (93.3 ± 8 mmHg) (Figure 1). The CO of the CLC group (3.4 ± 0.8 L/min) ($P < 0.01$) and the ALC group (3.7 ± 1.0 L/min) ($P < 0.01$) was significantly higher than that of the HV group (2.5 ± 0.5 L/min), while there was no significant difference of CO between the CH group (2.7 ± 0.4 L/min) and the HV group (Figure 2). The SVR of the CLC group (2518.6 ± 639 dynes*sec/cm^5) ($P < 0.05$) and the ALC group (2022.5 ± 502 dynes*sec/cm^5) ($P < 0.01$)

was significantly lower than that of the HV group (3064.3 $\pm$ 683 dynes*sec/cm^5), while there was no significant difference of SVR between the CH group (2631.4 $\pm$ 494 dynes*sec/cm^5) and the HV group (Figure 3).

Hemodynamic changes related to ascites in patients with HCV-related or alcoholic cirrhosis

To clarify whether there were any differences of the circulation in relation to the presence / absence of ascites in patients with LC, we divided to the CLC and ALC groups into non-ascitic and ascitic subgroups. In the CLC group, the mean BP of the non-ascitic (93.6 $\pm$ 10 mmHg) and ascitic (87.3 $\pm$ 14 mmHg) subgroups did not differ from that of the HV group, and there was no significant difference from that of the CH group. In the ALC group, the mean BP of the non-ascitic (91.8 $\pm$ 11 mmHg) and ascitic (81.5 $\pm$ 11 mmHg) subgroups also did not differ from that of the HV group (Figure 4). The CO of the non-ascitic (3.5 $\pm$ 0.7 L/min) and ascitic (3.0 $\pm$ 1.0 L/min) CLC subgroups was significantly higher than that of the HV group ($P < 0.05$), while there was no significant difference from that of the CH group. The CO of the non-ascitic (3.6 $\pm$ 1.0 L/min) and ascitic (3.8 $\pm$ 1.1 L/min) ALC subgroups was also significantly higher than that of the HV group ($P < 0.01$) (Figure 5). The SVR of both the non-ascitic (2114.2 $\pm$ 281 dynes*sec/cm^5) and ascitic (1917.8 $\pm$ 687 dynes*sec/cm^5) ALC subgroups was significantly lower than that of the HV group ($P < 0.01$). In contrast, there was no significant difference of SVR between the ascitic CLC subgroup (2754.6 $\pm$ 841 dynes*sec/cm^5) and the HV group, although that the SVR of the non-ascitic CLC

subgroup (2455.7 $\pm$ 595 dynes*sec/cm^5) was lower than that of the HV group (Figure 6).

HCI in patients with HCV-related or alcoholic cirrhosis

The mean PBF velocity of the ALC group (non-ascitic: 21.5 $\pm$ 6.4; ascetic: 17.0 $\pm$ 4.7 cm/sec) was lower than that of the HV group (23.4 $\pm$ 7.5 cm/sec), but not significantly. There was also no significant difference of the mean PBF velocity in CH group (26.7 $\pm$ 7.3 cm/sec) or the CLC group (non-ascitic: 26.0 $\pm$ 9; ascetic: 22.0 $\pm$ 4.5 cm/sec) compared with the HV group. However, the portal vein cross-sectional area of the ascitic ALC subgroup (1.02 $\pm$ 0.4 cm^2) was significantly larger than that of the HV group (0.60 $\pm$ 0.2 cm^2) ($P < 0.05$), although there was no significant difference between the non-ascitic ALC subgroup (0.88 $\pm$ 0.2 cm^2) and the HV group. The portal vein cross-sectional area of the CH group (0.77 $\pm$ 0.2 cm^2), the non-ascitic CLC subgroup (0.64 $\pm$ 0.4 cm^2), and the ascitic CLC subgroup (0.62 $\pm$ 0.3 cm^2) did not differ from that of the HV group. As a result, the HCI of the ascitic ALC subgroup (0.06 $\pm$ 0.02) was significantly higher than that of the HV group (0.03 $\pm$ 0.01) ($P < 0.05$), although there was no significant difference between the non-ascitic ALC subgroup (0.05 $\pm$ 0.01) and the HV group. The HCI of the CH group (0.03 $\pm$ 0.01), the non-ascitic CLC subgroup (0.03 $\pm$ 0.03), and the ascitic CLC subgroup (0.03 $\pm$ 0.01) also did not differ from that of the HV group (Figure 7).

Changes of the PBF volume and HVPG in patients with HCV-related or alcoholic cirrhosis

The PBF volume of the CH group (0.69 $\pm$ 0.2 L/min), the non-ascitic (0.84 $\pm$ 0.4 L/min) and ascitic (0.62 $\pm$ 0.1 L/min) CLC groups, and the non-ascitic (0.78 $\pm$ 0.4 L/min) and ascitic (0.72 $\pm$ 0.4 L/min) ALC groups did not differ from that of the HV group (0.71 $\pm$ 0.3 L/min) (Figure 8). The HVPG of the CLC and ALC groups was also not influenced by the presence / absence of ascites (Figure 9).

IV. DISCUSSION

Systemic hemodynamic changes are characterized by primary peripheral arterial dilatation and a secondary increase of cardiac output prior to the development of ascites in both experimental cirrhosis models and compensated cirrhosis in humans (1-3). There are two theories about how sodium and water retention occurs in cirrhosis. The classical "underfilling" theory proposes that hepatic venous obstruction and portal hypertension initially causes ascites in LC patients (11, 12). The other theory is that retention of sodium and water leads to "overflow" ascites secondary to hypervolemia and an increase of pressure in the portal system. This "overflow" hypothesis has been supported by many studies (13-17). However, the influence of the etiology of LC on hemodynamics is not well understood. In the present study, we examined patients with LC caused by HCV infection or alcoholism. LC is complicated by a hyperdynamic circulation that is characterized by generalized arterial dilatation, an increase of CO, normal or low arterial BP, and a decrease of SVR. Daimon et al. reported that the cardiac ejection fraction was not influenced by sex or age (18). However, the CO and SVR were normalized for body surface area because there were differences of sex and physique between the groups in present study. The CO of the CLC group and the ALC

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group was significantly higher than that of the HV group, while there was no significant difference of CO between the CH group and CLC group compared with the HV group. These findings indicate that systemic hemodynamics tend to deteriorate along with the progression of fibrosis in the liver. Systemic hemodynamic changes were more prominent in the ALC group than the CLC group because SVR was significantly lower in the ALC group.

To clarify whether there were any differences of the circulation in relation to the presence / absence of ascites, we divided each of the CLC and ALC groups into non-ascitic and ascitic subgroups. We found that the CO of the CLC or ALC groups was significantly higher than that of the HV group regardless of the appearance of ascites, while there was no significant difference from that of the CH group. However, the SVR of the ALC group was significantly lower than that of the HV group regardless of the presence of ascites, although there was no significant difference of SVR between CLC subgroup and the HV group. It has been reported that the mean endotoxin level is significantly higher in ALC patients than non-ALC patients (19). It has also been reported that endotoxin decreases the mean arterial BP and increases the central venous pressure and heart rate (20). Furthermore, endotoxemia may induce nitric oxide synthesis and thus increase nitric oxide production and vasodilatation(21). Chin-Dusting et al. reported that peripheral vasodilatation in patients with cirrhosis was associated with an increase of nitric oxide synthesis (22). Our results indicated that the SVR of the ALC group was one of the important differences in hemodynamics among the groups since alcohol induces peripheral vasodilatation, although the decrease of SVR was not related to the appearance of ascites.

In the present study, there was no significant difference of the mean PBF velocity between each LC group and the HV group. However, the portal vein cross-sectional area of the ascitic ALC subgroup was significantly larger than that of the HV group, although there was no significant difference between the non- ascitic ALC subgroup and the HV group. As a result, the HCI of the ascitic ALC subgroup was significantly higher than that of the HV group, although there was no significant difference between the non-ascitic ALC subgroup and the HV group. In alcoholic liver disease (ALD), fibrosis around central hepatic veins and perihepatocytes and ballooning of hepatocytes lead to portal hypertension. Spontaneous reversal of portal blood flow sometimes occurs as a result of a large intrahepatic arterioportal fistula or portosystemic shunting in ALC (23). Bolognesi et al. found different hemodynamic patterns in patients with advanced cirrhosis of alcoholic or viral origin and reported that more marked alteration of intrahepatic portal perfusion and a higher liver weight were associated with ALC (24). We have investigated the characteristics of blood flow within the hepatic parenchyma of patients with ALD by contrast-enhancd ultrasound. As a result, we suggested that arterialization of the liver and intrahepatic shunting among the branches of the hepatic arteries, portal veins, and hepatic veins occur in ALD patients before the onset of cirrhosis, and that these changes occur earlier in ALD than in viral liver disease (25). In the present study, SVR was much lower in the ALC group than in the HV group, although PBF was maintained despite the existence of portosystemic collaterals, but the HCI was much higher in the ALC group. These patients may have hyperdynamic portal venous circulation, especially in the veins running from the abdominal organs and from the enlarged spleen in portal hypertensive patients (26, 27). It has been reported that the

HVPG was significantly higher in Child-Pugh class B and C patients (28) and that the extent of the decrease of HVPG with pharmacological treatment predicts the risk of rebleeding, ascites, peritonitis, hepatorenal syndrome, encephalopathy, and death (29, 30). However, it has not been reported whether an increase of HVPG directly influences the appearance of ascites in patients with CLC or ALC. Our results might suggest that the decrease of SVR in the ALC group is due to the effect of nitric oxide, while the increase of HCI in the ALC group is caused by arterialization or intrahepatic shunts. However, there was no difference of HVPG among CLC or ALC patients regardless of the presence / absence of ascites. In the ALC group, therefore, an increase of the HCI might be important in the appearance of ascites.

In conclusion, the progression of liver disease (ALC or CLC) leads to a hyperdynamic circulation characterized by increased CO and decreased SVR. The increase of HCI is marked in ALC patients with ascites, while there is no change of HCI in CLC patients regardless of whether or not they have ascites. These results indicate that the HCI may be important in the onset of acsites, that there is a greater excess of hepatic arterial blood flow over portal flow in ALC patients compared with CLC patients, and that arterialization or intrahepatic shunting is much more patients in ALC than in CLC.

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Figure legends

Fig.1   Comparison of the mean blood pressure among the CH, CLC, ALC, and HV groups. There were no significant differences among these groups.

Fig.2   Comparison of cardiac output among the CH, CLC, ALC, and HV groups. The cardiac output of the CLC and ALC groups was significantly higher than that of the HV group (**: $P < 0.01$, Dunnet's test).

Fig.3   Comparison of systemic vascular resistance among the CH, CLC, ALC, and HV groups. The systemic vascular resistance of the CLC and ALC groups was significantly lower than that of the HV group (*: $P < 0.05$, **: $P < 0.01$, Dunnet's test).

Fig.4 Comparison of the mean blood pressure among the CH group, non-ascitic and ascitic CLC subgroups, non-ascitic and ascetic ALC subgroups, and HV group. There were no significant differences among these groups.

Fig.5   Comparison of cardiac output among the CH group, non-ascitic and ascitic CLC subgroups, non-ascitic and ascitic ALC subgroups, and HV group. The cardiac output of the non-ascitic CLC subgroups was significantly higher than that of the HV group, while that of both ALC subgroups was significantly higher than in the HV group (*: $P < 0.05$, **: $P < 0.01$, Dunnet's test).

Fig.6   Comparison of systemic vascular resistance among the CH group, non-ascitic

and ascitic CLC subgroups, non-ascitic and ascitic ALC subgroups, and HV group. The systemic vascular resistance of the non-ascitic CLC subgroups was significantly lower than that of the HV group, while both ALC subgroups had significantly lower resistance than the HV group (*: $P < 0.05$, **: $P < 0.01$, Dunnet's test).

Fig.7   Comparison of the mean portal blood flow velocity, the cross-sectional area of the main portal vein, and the hepatic congestion index among the CH group, non-ascitic and ascitic CLC subgroups, non-ascitic and ascitic ALC subgroups, and HV group. There were no significant differences of mean portal blood flow velocity among these groups. The portal vein cross-sectional area was significantly larger in the ascitic ALC subgroup than in the HV group (*: $P < 0.05$, Dunnet's test). The hepatic congestion index was significantly higher in the ascetic ALC subgroup than that in the HV group (*: $P < 0.05$, Dunnet's test).

Fig.8   Comparison of portal blood flow volume among the CH, CLC, ALC, and HV groups. There were no significant differences among these groups.

Fig.9   Comparison of the hepatic venous pressure gradient between the non-ascitic or ascitic subgroups of the CLC or ALC group. There were no significant differences in relation to the presence of ascites.