Diurnal Fluctuations of Portal and Systemic Hemodynamic Parameters in Patients with Cirrhosis

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A close temporal relationship between higher levels of portal pressure during the night and the peak incidence of acute variceal bleeding has recently been demonstrated in patients with cirrhosis. Because hemodynamic changes may have a role in triggering this hemorrhagic episode, we measured systemic and portal hemodynamic parameters at 4-hr intervals for 24 hr in 12 cirrhotic patients. These results were compared with those obtained in eight healthy subjects. Cardiac output, femoral and portal blood flows were measured by Doppler technique. In cirrhotic patients, heart rate and mean arterial pressure remained constant throughout the whole study period. A marked and significant increase in portal blood flow (917 ± 248 ml/min) (mean ± S.D.) as compared with mesor values (649 ± 114 ml/min, $p < 0.001$) was observed at midnight. This effect was accompanied by a mild but significant rise of cardiac output (from 6.5 ± 0.7 to 6.8 ± 0.7 l/min, $p < 0.01$) at 2400 hr. A significant correlation between both hemodynamic parameters was found ($r = 0.78$, $p < 0.01$). Cosinor analysis showed a significant ($p < 0.05$) circadian rhythm for both portal blood flow and cardiac output with an acrophase at 0050 hr. In the healthy subjects group, a significant decrease of mean arterial pressure and heart rate was observed at 2400 hr. Cosinor analysis confirmed the presence of significant rhythm for both hemodynamic parameters. In contrast with cirrhotic patients, no significant changes were observed in portal blood flow and cardiac output in healthy subjects. Our results show that in patients with cirrhosis, maximal increases in portal blood flow occur at night. The circadian variation of portal blood flow could have important implications in the management of these patients. (HEPATOLOGY 1994;20:1198-1203.)

Clinical and experimental evidence has shown that chronic liver disease is usually accompanied by deep disturbances of the circadian organization, such as changes in the rest-activity cycle (1) and the diurnal profile of hormone levels (2). It has also been reported that rats undergoing portacaval anastomosis showed changes in rhythmic patterns, such as variations in the melatonin rhythm secretion (3, 4). Collectively, these findings suggest that a variety of other circadian rhythms could be altered in chronic liver disease.

A circadian variation in portal pressure has been demonstrated in patients with cirrhosis, with high levels at night (5). This deleterious effect was also accompanied with a greater risk of acute variceal bleeding, with a peak incidence between 2000 hr and 0100 hr (5), thus suggesting a close temporal relationship between the hemodynamic and clinical variables. Similar results regarding the time of occurrence of acute gastrointestinal bleeding have recently been reported by other authors (6, 7). Therefore, the purpose of this study was to investigate the possible daily fluctuation of hemodynamic parameters in patients with cirrhosis, and the systemic results were also correlated with simultaneous changes in portal blood flow. These results compared with those of age-matched, normal, healthy volunteers.

MATERIALS AND METHODS

Subjects. Twelve cirrhotic patients (10 men, 2 women; mean age, 57 yr; range, 30 to 71 yr) were studied. The diagnosis of liver disease was made on the basis of clinical and laboratory data, together with liver biopsy when it was available. Cirrhosis was alcoholic in 10 patients and posthepatitic in two patients. All patients with cirrhosis had severe portal hypertension, as evidenced by the presence of esophageal varices, shown by endoscopy. Eight patients had previously bled from varices, and two had mild ascites. Child-Pugh's quantitative score was 7.1 ± 2.8. Eight control subjects (five men, three women; mean age, 50 yr; range, 25 to 65 yr) were also studied. None of them had a positive history or evidence of renal, hepatic, or cardiovascular disease. Portal hypertensive patients and healthy subjects were taking no form of vasoactive medication. Written consent was obtained from each subject participating in this study, which was approved by the hospital ethics committee.

24-hour Study. Cirrhotic patients were admitted to hospital 4 days before the hemodynamic study. During this time, patients underwent an acclimation period in a quiet room with a temperature of 20° to 24° C. Doppler measurements were performed on three consecutive days at 8 A.M. after overnight fast. This three-day period was used as a test for intrasubject

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TABLE 1. Systemic and portal hemodynamic parameters in 12 cirrhotic patients

Parameters	24-Hour clock study					
	0800	1200	1600	2000	2400	0400
Heart rate (beats/min)	77 ± 4	77 ± 4	78 ± 4	79 ± 4	78 ± 4	78 ± 4
Mean arterial pressure (mmHg)	90 ± 12	90 ± 11	88 ± 12	89 ± 12	89 ± 13	90 ± 10
Cardiac output (l/min)	6.2 ± 0.7	6.2 ± 0.8	6.3 ± 0.8	6.3 ± 0.7	6.8 ± 0.7[a]	6.6 ± 0.9
Peripheral vascular resistance (dyne · sec · cm^{-5})	1170 ± 230	1165 ± 200	1110 ± 221	1145 ± 224	1050 ± 228	1080 ± 197
Femoral blood flow (ml/min)	322 ± 84	329 ± 78	308 ± 53	359 ± 96	356 ± 108	333 ± 72
Portal blood flow (ml/min)	603 ± 110	680 ± 179	632 ± 179	631 ± 169	917 ± 248[b]	697 ± 178

[a] $p < 0.01$ in regard to mesor values.
[b] $p < 0.001$ in regard to mesor values.
Values expressed as mean ± S.D.

and intraobserver variability of repeated hemodynamic measurements. The coefficient of variation of these measurements was calculated as (1 S.D./mean × 100). On the day of the study, systemic and portal hemodynamic parameters were measured at 0800, 1200, 1600, 2000, 2400 and 0400 hr. During this 24-hr period the patients pursued their ordinary activities within the room. Hemodynamic studies were performed at least 2 hr after meals and after at least 30 min of rest in supine position. Measurements at the middle of the night were performed after a fixed interval of 15 min after wake up. A similar schedule was used for the control subjects group.

To study the reproducibility of the hemodynamic findings, systemic and splanchnic parameters were reevaluated in four of the 12 cirrhotic patients 18 ± 6 days after the first study, under the same conditions as previously mentioned.

Measurement of Hemodynamic Parameters. Blood flow was measured by a duplex scanner (Toshiba, Sonolayer SSA 270 A), comprising a real-time, two-dimensional ultrasonic scanner and an associated 3.5 MHz pulsed Doppler flowmeter. After a sampling marker had been set in the middle of the lumen (portal vein and femoral artery) along the beam axis, a second marker was positioned parallel to the direction of blood flow.

Care was taken to maintain the angle Θ (the angle formed by the ultrasonic beam and blood flow direction) below 60°, because the accuracy of the hemodynamic measurements decreases with greater angles. Measurements were carried out during expiration, because it can be easily standardized and permits a better visualization of the portal vein for Doppler purposes, as the angle Θ is reduced to a minimum. Blood flow (ml/min) rates were obtained by multiplying the blood velocity (cm/seg) by the cross-sectional area of the vessel (mm), calculated on the basis of the inner diameter, assuming circular geometry. Doppler assessment of the left ventricular ejection velocity was obtained by positioning the sample marker in the aorta just distal to the aortic valve on a B-mode, four-chamber image plus aorta image with the transducer placed on the apical zone. This position makes the angle between the ultrasound beam and the direction of blood stream near zero. Doppler evaluation was always carried out by the same specialized examiner (D.A.).

Arterial pressure (mmHg) was measured with a sphygmomanometer and was expressed as mean arterial pressure according to the formula: (systolic pressure + diastolic pressure × 2) ÷ 3. Systemic vascular resistance (dyne · sec · cm^{-5}) was calculated as (mean arterial pressure/cardiac output) × 80.

Statistical Analysis. Hemodynamic measurements were performed in triplicate for each time point. Results are expressed as mean ± S.D. Data were analyzed using the repeated ANOVA test followed by Tukey Kramer multiple comparisons test; correlation was performed by means of Pearson's coefficient. Cosinor analysis (8) was used to specify circadian rhythm parameters of the series. Briefly, cosinor analysis adjusts the data to a cosine waveform and describes the rhythm's amplitude (half the difference between the highest and lowest point in the cosine curve), acrophase (the time at which the highest value of the adjusted cosine function occurs, expressed as a lag from zero time) and mesor (midline estimate statistic of rhythm; i.e., rhythm-determined average of the value midway through the highest and lowest values of the sinusoidal curve). In this study, cosine curve parameters and ANOVA differences were considered significant when p was less than 0.05.

RESULTS

The variability of the Doppler technique was assessed by a single observer (D.A.), performing multiple cardiac output and portal and femoral blood flow measurements in the same patients on three consecutive days at 0800 hr. For each recording the coefficient of variation was less than 6%, thus demonstrating a high degree of reproducibility for the methodology used.

Systemic and hemodynamic parameters determined in the cirrhotic patients throughout the day are shown in Table 1. Heart rate and mean arterial pressure remained constant throughout the whole study period (Table 1). Cardiac output at 2400 hr was significantly higher than mesor value (Tables 1 and 2). Cosinor analysis showed that circadian acrophase of cardiac output was located at midnight (Table 2). No significant temporal changes were observed in peripheral vascular resistance (Table 1), whereas a mild but not significant increase in femoral blood flow was also observed at 2400 hr (Table 1).

A marked increase in portal blood flow (917 ± 248 ml/min), as compared with mesor values (649 ± 114 ml/min, $p < 0.001$) was observed in cirrhotic patients at 2400 hr (Fig. 1). The increase in portal blood flow was entirely due to a significant rise in mean blood velocity, with no time-related change in the caliber of the portal vein (Fig. 1). As shown in Figure 2, this effect was maximal at midnight in all except one patient. Cosinor analysis showed that portal blood velocity and flow had a significant circadian rhythm, with an acrophase at

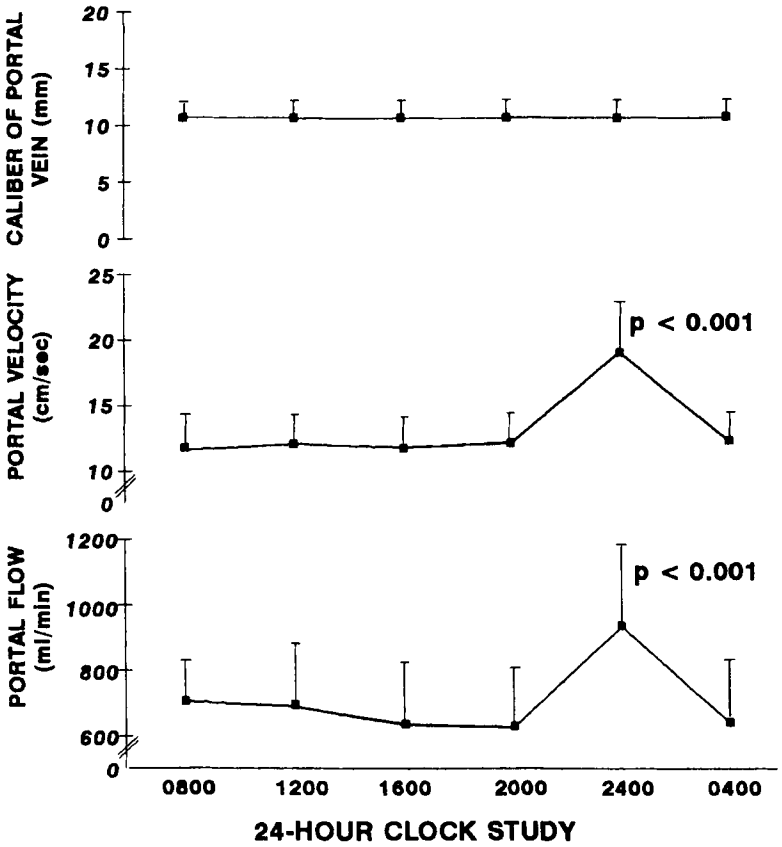

FIG. 1. Twenty-four-hour profile of portal hemodynamic parameters in patients with cirrhosis. Note that the increase in portal blood flow was entirely due to a significant rise in portal velocity with no time-related change in the caliber of the portal vein. A circadian rhythm was also exhibited for both hemodynamic parameters, with the highest levels during nocturnal period. The significant levels are expressed as mesor values.

0050 hr (Table 2). Although the nocturnal increase in portal blood flow was greater than that of the cardiac output ($p < 0.01$), a significant correlation between both hemodynamic parameters was observed ($r = 0.78$, $p < 0.01$).

Table 3 shows systemic and splanchnic hemodynamic parameters in the four reevaluated cirrhotic patients. Heart rate and mean arterial pressure did not change throughout the day. A parallel increase in cardiac output and portal blood flow at 24 hr was observed in each cirrhotic patient studied (Table 3). No temporal changes were seen in peripheral vascular resistance and femoral blood flow (Table 3).

In the control group, a significant decrease with respect to mesor values of mean arterial pressure and heart rate was observed at 2400 hr (Table 4). Cosinor analysis confirmed the presence of a significant circadian rhythm for both hemodynamic parameters. In contrast with cirrhotic patients, no significant changes were observed in portal blood velocity and flow or cardiac output in control subjects (Table 4).

DISCUSSION

Our study shows the occurrence of a daily fluctuation in portal and systemic hemodynamic parameters in patients with cirrhosis, with portal blood flow and cardiac output peaking toward the middle of the night.

Variceal hemorrhage is a major clinical problem in patients with cirrhosis. It is therefore necessary to gain further insight into the mechanism(s) responsible for its occurrence, so that preventive measures may be taken. Recent studies have shown a diurnal pattern in the time of onset of acute gastrointestinal bleeding in patients with cirrhosis (5-7). A greater incidence of bleeding from sources related to portal hypertension was observed during night hours (5-7).

A number of different hemodynamic factors may play a role in the circadian variation of variceal bleeding in patients with cirrhosis. Higher portal pressure levels have been observed during the night (5), demonstrating a close temporal relationship between the clinical and hemodynamic events. To our knowledge, our study represents the most complete description of the circadian variation of portal and systemic hemodynamic parameters in patients with cirrhosis. Regarding the technique used, several reports from our laboratory (9) and others (10, 11) point out that Doppler ultrasound measurements are quite reproducible and actually useful to monitor response to physiological and pharmacological stimuli in patients with cirrhosis. In this

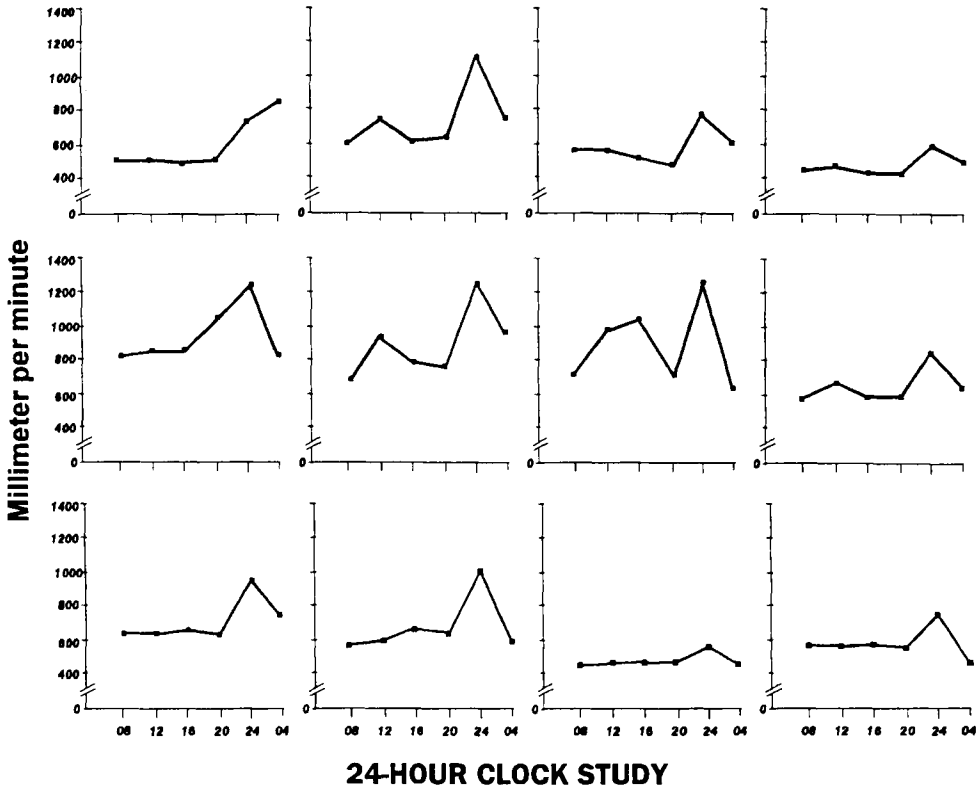

FIG. 2. The figure shows individual portal blood flow values in 12 cirrhotic patients. Note that portal blood flow increased in all but one patient at midnight.

TABLE 2. Circadian data for portal and systemic hemodynamic parameters in cirrhotic patients

Parameters	Acrophase[a] (95% CL)	Mesor[b]	Amplitude[c]	p Value of rhythm
Cardiac output (l/min)	0.1 A.M. (0.0-0.2)	6.5 ± 0.7	0.4 ± 0.2	0.05
Portal blood velocity (cm/sec)	0.5 A.M. (0.4-0.6)	14.2 ± 2.1	2.4 ± 0.9	0.05
Portal blood flow (ml/min)	0.5 A.M. (0.4-0.6)	649 ± 114	131 ± 61	0.05

[a]*95% CL*, 95% confidence limits; *Acrophase*, peak time of circadian period.
[b]*Mesor*, mean value over circadian period.
[c]*Amplitude*, difference between mesor and high- or low-value circadian period.
Values expressed as mean ± S.D.

study, day-to-day Doppler measurements were highly reproducible for each cirrhotic patient.

Our results show that portal blood flow varies rhythmically in patients with cirrhosis, with an acrophase near midnight. This effect was mainly the result of a significant increase in portal blood velocity. Moreover, a close relationship between changes in portal blood flow and cardiac output was found. As the increase in nocturnal blood flow was greater than that in cardiac output, it may be suggested that the higher blood flow levels during the night are not only caused by a greater cardiac output, but a splanchnic vasodilation factor may also be involved.

The mechanism by which portal blood flow increases during the night in patients with cirrhosis is unknown. It is possible that blood flow variations may be related to changes in cardiovascular regulatory mechanisms during the night resulting from humoral and/or neurogenic factors. The observed effect could be due, at least in part, to: (a) an increased amplitude of the rhythm of vasodilator component(s); (b) a decreased amplitude of rhythm of vasoconstrictor mechanism(s); (c) a combination of both. With regard to the first point, recent studies have shown that VIP and CGRP, two powerful endogenous vasodilators that are present in higher levels in patients with chronic liver disease (12, 13), exhibit a circadian rhythm with midnight peaks in healthy subjects (14, 15). On the other hand, the nocturnal increase of portal blood flow might also reflect a reduction of sympathetic activity. This latter explanation is supported by the fact that lower catecholamine levels are found during the night in normal subjects (16). Bernardi et al. (2) have shown an impairment of circadian rhythmicity of sympathetic activity in patients

TABLE 3. Systemic and portal hemodynamic parameters in the four reevaluated cirrhotic patients

Parameters	24-hour clock study					
	0800	1200	1600	2000	2400	0400
Heart rate (beats/min)	79 ± 4[a]	79 ± 4	81 ± 4	81 ± 2	81 ± 4	81 ± 4
Mean arterial pressure (mm Hg)	91 ± 12	92 ± 10	89 ± 10	91 ± 8	92 ± 8	92 ± 8
Cardiac output (L/min)	6.3 ± 0.4	6.5 ± 0.2	6.4 ± 0.2	6.4 ± 0.2	7.1 ± 0.6	7.1 ± 0.6
Peripheral vascular resistance (dyne · sec · cm^{-5})	1167 ± 148	1130 ± 128	1113 ± 114	1129 ± 136	1053 ± 144	1049 ± 146
Femoral blood flow (ml/min)	307 ± 48	330 ± 64	321 ± 44	353 ± 74	379 ± 110	340 ± 54
Portal blood flow (ml/min)	538 ± 54	586 ± 94	506 ± 66	531 ± 72	791 ± 156	675 ± 104

Statistical analysis was not performed because of small number of cirrhotic patients.
[a]Values expressed as mean ± S.D.

TABLE 4. Systemic and portal hemodynamic parameters in eight healthy subjects

Parameters	24-hour clock study					
	0800	1200	1600	2000	2400	0400
Heart rate (beats/min)	74 ± 6[a]	75 ± 6	75 ± 6	76 ± 3	62 ± 3[a]	64 ± 6
Mean arterial pressure (mmHg)	95 ± 6	92 ± 3	95 ± 3	94 ± 6	86 ± 6[a]	86 ± 6
Cardiac output (l/min)	5.0 ± 0.3	4.9 ± 0.3	5.0 ± 0.3	4.9 ± 0.3	5.0 ± 0.3	5.0 ± 0.3
Peripheral vascular resistance (dyne · sec · cm^{-5})	1536 ± 151	1545 ± 143	1584 ± 143	1547 ± 162	1393 ± 140	1382 ± 143
Femoral blood flow (ml/min)	248 ± 39	264 ± 31	282 ± 53	269 ± 42	243 ± 31	243 ± 31
Portal blood flow (ml/min)	739 ± 157	732 ± 143	734 ± 132	754 ± 157	746 ± 143	739 ± 148

$p < 0.05$ vs. mesor values.
[a]Values expressed as mean ± S.D.

with cirrhosis. In this study, the physiological drop in adrenergic tone, observed in control subjects (16), is absent in patients with cirrhosis (2). Alternatively, it is also possible that hemodynamic changes may be related to some type of dysfunction of the central nervous system. In the past few years, several central-acting drugs and endogenous substances have been shown to affect the mammalian circadian clock. Special attention has been drawn to two of these agents, melatonin (17, 18) and bensodiazepines (19, 20), that may act through central GABAergic receptors (21). It should be pointed out that GABA-BZD receptor activity and endogenous ligand levels (22) have been related to the pathogenesis and treatment of chronic liver failure, particularly regarding hepatic encephalopathy. It can be argued that sleep disruption that takes place during night measurements affects hemodynamic parameters. This fact seems unlikely because an identical schedule was applied to both control and cirrhotic groups, so that the observed effect is probably related to liver disease. However, the possibility of the difference in the sensitivity of hemodynamic parameters resulting from sleep disruption between both groups cannot be ruled out.

From a clinical point of view, the findings summarized in this article might have several consequences. First, when systemic and splanchnic hemodynamic measurements are performed in cirrhotic patients, it is necessary to take into account the time at which the parameter is measured. Second, our results indicate that maximal hemodynamic changes occur during the night, perhaps accounting for the higher risk of variceal bleeding. Further studies should be undertaken in order to assess whether the effect of drugs applied in the pharmacological treatment of portal hypertension might depend on their time of administration. Our study confirms that mean arterial pressure and heart rate are subjected to diurnal variations in control subjects (23, 24). However, in contrast with those observed in patients with cirrhosis, no temporal changes in cardiac output and portal blood flow were observed in control subjects, demonstrating that these hemodynamic variations are exclusively related to liver diseases. Our results suggest that the lack of diurnal profiles of mean arterial pressure and heart rate, as shown by Bernardi et al. (2), as well as the nocturnal increase in cardiac output and portal blood flow seen in patients with cirrhosis, could be some of the deep disturbances of the circadian organization associated with chronic liver diseases.

Finally, we hypothesize that cirrhotic patients who show substantial variations in portal blood flow during the night may have a higher probability of development of a variceal hemorrhage at this particular time. This could, in part, explain the reported increased incidence of variceal bleeding at night.

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