Is small intestinal bacterial overgrowth a cause of hyperdynamic circulation in cirrhosis?

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ABSTRACT

Background/Aims: *Small intestinal bacterial overgrowth (SIBO) and hemodynamic changes are common in cirrhosis. We wanted to examine our hypothesis whether SIBO leads to hemodynamic changes in cirrhosis.*

Materials and Methods: *A total of 50 patients with cirrhosis and 15 healthy controls were enrolled in a pilot prospective study. All participants underwent the lactulose hydrogen breath test for SIBO and echocardiography with a simultaneous assessment of blood pressure and heart rate. Cardiac output and systemic vascular resistance were calculated.*

Results: *Study participants with SIBO had a lower systolic blood pressure and systemic vascular resistance compared to those without SIBO and to healthy controls (110.2±12.3 mmHg vs. 126.2±21.0 mmHg and 121.2±9.8 mmHg; p=0.005 and p=0.011, respectively; 1312±352 dyn·s·cm^{-5} vs. 1704±424 dyn·s·cm^{-5} and 1648±272 dyn·s·cm^{-5}; p=0.001 and p=0.006, respectively), but a higher cardiac output (5.38±1.41 l/min vs. 4.52±1.03 l/min and 4.40±0.68 l/min; p=0.034 and p=0.041, respectively) and C-reactive protein (10.5[1.2-16.5] mg/l vs. 2.8[0.6-9.1] mg/l; p=0.028; no comparison with healthy controls). There were no significant differences between patients without SIBO and healthy controls with regard to systolic blood pressure (p=0.554), systemic vascular resistance (p=0.874), and cardiac output (p=0.795). SIBO was associated with vasodilation and hyperdynamic circulation in decompensated cirrhosis (p=0.002; p=0.012), but not in compensated cirrhosis (p=1.000; p=0.474).*

Conclusions: *SIBO is associated with hyperdynamic circulation and other hemodynamic changes in cirrhosis and may be a principal factor causing these through systemic inflammation.*

Keywords: *Cirrhosis, vasodilation, gut microbiota, hemodynamics, systemic inflammation*

INTRODUCTION

Hemodynamic changes in cirrhosis include an abnormally increased cardiac output, increased total blood volume, decreased blood pressure, and decreased systemic vascular resistance (1,2). Together, these changes constitute hyperdynamic circulation. Vasodilatation and hyperdynamic circulation are believed to cause complications of cirrhosis, which include portal hypertension, hepatorenal and hepatopulmonary syndromes, and hepatic encephalopathy (3).

Bacterial translocation, which is the passage of bacteria and bacterial components from the intestinal lumen into the intestinal wall, mesenteric lymph nodes, and portal and systemic circulation, is thought to play a principal role in the pathogenesis of hyperdynamic circulation by causing systemic inflammation in patients with cirrhosis (4-6).

Detection of bacterial translocation in real clinical practice is very difficult because of lack of reliable biomarkers (4). Predisposing factors for the development of bacterial translocation in cirrhosis are small intestinal bacterial overgrowth (SIBO), gut dysbiosis, increased intestinal permeability, and impaired function of the gut mucosa-associated immune system. The contribution of each of these factors to the development of bacterial translocation is still unclear (5).

Despite the increased focus on gut dysbiosis, the clinical significance of the alteration of the gut microbiome in cirrhosis has not been established yet. Methods for determining gut dysbiosis have not been introduced in clinical practice, and we do not know how to reliably manage gut dysbiosis.

In real clinical practice, SIBO is the only factor of bacterial translocation that we can diagnose and manage (7).

SIBO is common in cirrhosis (8-13). However, we do not know whether SIBO influences hemodynamic changes in cirrhosis. Therefore, we conducted this pilot study to test our hypothesis whether SIBO had an impact on hemody-

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namic parameters that might be caused by systemic inflammation without development of an evident infection.

MATERIALS AND METHODS

Participants

This cross-sectional prospective study was run from March 2016 to December 2016. It was approved by the clinical research ethics committee and was conducted in accordance with the Declaration of Helsinki.

The study aim and procedures were explained to prospective participants, and written informed consent was obtained before their enrolment. We considered for inclusion people of both genders, and at least 18 years of age, who were diagnosed with cirrhosis on clinical, biochemical, and ultrasound findings, and further verified by histology. We excluded people who had been treated with lactulose, lactitol, or other prebiotics, probiotics, antibiotics, or prokinetics or consumed alcohol in the past 6 weeks, and had current infection or diabetes, inflammatory bowel disease, cardiac disease, cancer, or any other disease considered to be severe.

A total of 113 people with cirrhosis were screened in consecutive order for participation in this study, and only 50 met the inclusion criteria and were enrolled in the study (Figure 1).

Fifteen healthy individuals who visited our clinic for routine physical examinations during the same time period were invited to participate in our study as controls and their written informed consent was also obtained. The aims and procedures of the study were explained.

Clinical characteristics of enrolled participants with cirrhosis are presented in Table 1.

Diagnostic workup

We determined the severity of liver disease in the study participants using the Child-Turcotte-Pugh (CTP) scoring system in which Class A is defined as compensated

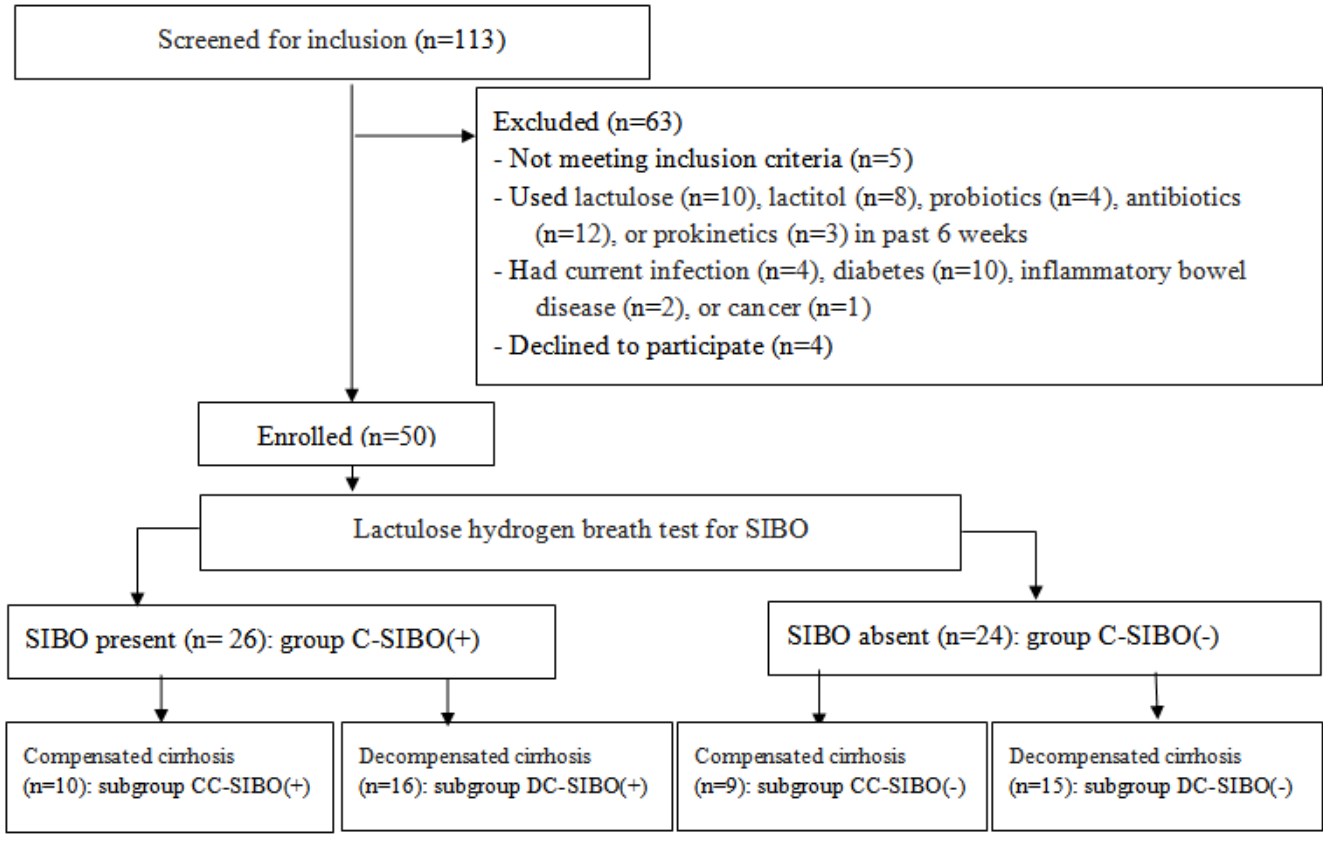

Figure 1. *Flow chart of study participants.*

Table 1. Main characteristics (mean±standard deviation) and frequency of detection of SIBO by etiology of cirrhosis in the 50 enrolled participants with cirrhosis.

	SIBO(+) group (n=26)	SIBO(-) group (n=24)	p
Age, years	49.1±12.9	48.7±13.3	0.904
Body mass index, kg/m^2	25.2±4.2	24.7±3.2	0.636
Men/women	13/13	11/13	0.785
Race (Caucasian/other)	25/1	24/0	1.000
Etiology of cirrhosis: alcohol	9	9	1.000
autoimmune	2	9	0.016
viral	11	6	0.242
cryptogenic	4	0	0.111
Child-Turcotte-Pugh Score	8.31±2.40	7.83±2.14	0.465
Model for End-Stage Liver Disease Score	10.9±5.0	10.4±6.1	0.317
Esophageal varices (present/absent)	20/6	20/4	0.728
Hepatic encephalopathy (overt/minimal/ absent)	9/9/8	8/11/5	0.526
Ascites (present/absent)	18/8	10/14	0.086
Serum albumin, g/L	34.5±6.1	35.6±6.0	0.505
Prothrombin index (quick test), %	58.1±11.4	63.8±16.0	0.146
Creatinine, mg/dL	0.77±0.25	0.77±0.27	0.949
RBC, cell/μL	3.77±0.72	3.92±0.53	0.393
WBC, cell/μL	4.26±2.12	4.61±2.32	0.579
Platelets, cell/μL	80.6±43.6	99.1±42.6	0.136
Erythrocyte sedimentation rate, mm/h	18.5±13.3	18.5±16.2	1.000
Splenic length, cm	16.8±3.0	15.3±3.0	0.112
Blood culture (positive/negative)	0/26	0/24	1.000
Urine culture (positive/negative)	0/26	0/24	1.000
Ascitic fluid culture (positive/negative)	0/12	0/6	1.000
Medication used before admission (yes/no): proton pomp inhibitors	10/16	9/15	1.000
beta-blockers	5/21	3/21	0.704
ornithine-aspartate	4/22	4/20	1.000
diuretics	14/12	9/15	0.272
ursodeoxycholic acid	4/22	6/18	0.490
steroids	2/24	6/18	0.132
antiviral drugs	8/18	4/20	0.327
antibiotics	0/26	0/24	1.000
lactulose or lactitol	0/26	0/24	1.000

Significant differences are marked in bold italics.

Table 2. Calculations of hemodynamic parameters.

Parameter	Calculation
Left ventricular mass index	(0.8×1.04×(((interventricular septum)+(left ventricular internal dimension)+(posterior wall of left ventricle))3-(left ventricular internal dimension)3)+0.6)/body surface area (17,20)
End-diastolic volume and end-systolic volume of the left ventricle	Modified Simpson's disk method
Ejection fraction of the left ventricle	((end-diastolic volume)-(end-systolic volume))/(end-diastolic volume)
Stroke volume	(Doppler velocity time integral)×(cross-sectional aorta area) (21)
Pulse pressure	(systolic blood pressure)-(diastolic blood pressure)
Mean arterial pressure	((systolic blood pressure)+2×(diastolic blood pressure))/3
Cardiac output	(stroke volume)×(heart rate)
Systemic vascular resistance	(mean arterial pressure)/(cardiac output)
Total arterial compliance	(stroke volume)/(pulse pressure) (17)
Systolic pulmonary artery pressure	(right atrium pressure estimated from diameter of inferior vena cava and respiratory changes)+4×(the peak velocity of the tricuspid valve regurgitant jet)2 (18-19)
Mean pulmonary artery pressure	0.61×(systolic pulmonary artery pressure)+2 mmHg (22)

cirrhosis, and Classes B and C are defined as decompensated cirrhosis (14).

In addition, we obtained blood samples from all participants with cirrhosis after 12 hours of fasting and rest on the day after the recruitment to measure the plasma C-reactive protein (CRP). The breath test for SIBO and echocardiography were performed on the same day.

We diagnosed SIBO using a lactulose hydrogen breath test in accordance with the North American Consensus, where it is recommended that glucose or lactulose breath tests are to be used to diagnose SIBO (15).

We used a Gastrolyzer (Bedfont, The United Kingdom) to measure the breath samples. We followed manufacturer's instructions and considered the presence of SIBO when there was an increase in breath hydrogen of at least 20 ppm above the baseline value with two consecutive readings within a 2-hour period (15).

Echocardiography

Echocardiography was performed at rest according to the guidelines published by the American Society of Echocardiography (16-19). The systolic and diastolic blood pressure and heart rate were measured together with the stroke volume using automatic oscillometric sphygmomanometer (AND, Japan). Calculations of hemodynamic parameters are presented in Table 2.

Because the normal ranges of cardiac output and systemic vascular resistance strongly depend on the method, we derived the normal ranges of cardiac output and systemic vascular resistance from the minimum and maximum range values in our control group. If the cardiac output of a participant with cirrhosis was higher than the normal range, we assumed that the person had hyperdynamic circulation. If the participant's systemic vascular resistance was lower than the normal range, we assumed that the person had arterial vasodilatation.

Statistical analysis

A statistical analysis was performed with the STATISTICA 10 software (StatSoft Inc.; USA). The difference between continuous variables was assessed using the Mann-Whitney test. Data were presented as mean±-standard deviation, except for the CRP concentration, which was presented as median (interquartile range). The correlation between variables was computed using Spearman's rank correlation (in correlation with CRP values) and Pearson's correlation in other cases. Fisher's exact test was used to assess the difference between

categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

The mean values of the 50 participants with cirrhosis and 15 healthy controls were comparable with regard to age (48.9±12.9 years vs. 46.7±7.7 years; p=0.541); body mass index (25.0±3.4 kg/m^2 vs. 26.2±4.5 kg/m^2; p=0.278); and sex distribution (male/female: 24/26 vs. 6/9; p=0.789).

SIBO was detected in 26 participants with cirrhosis (52% of total), hereto referred to as group C-SIBO(+). Participants with cirrhosis but without SIBO are hereto referred to as group C-SIBO(-) (Figure 1). Groups C-SIBO(+) and C-SIBO(-) were comparable in age, body mass index, gender distribution, severity of cirrhosis, and other characteristics (Table 1).

Nineteen participants with cirrhosis had compensated cirrhosis (CTP Class A), and the remaining 31 had decompensated cirrhosis (19 CTP Class B and 12 CTP Class C). SIBO was detected in 52.6% of participants with compensated cirrhosis (10 out of 19) and in 51.6% of participants with decompensated cirrhosis (16 out of 31, p=1.000). People with compensated cirrhosis with SIBO formed subgroup CC-SIBO(+), while people with decompensated cirrhosis with SIBO formed subgroup DC-SIBO(+). People with compensated cirrhosis without SIBO formed subgroup CC-SIBO(-), while people with decompensated cirrhosis without SIBO formed subgroup DC-SIBO(-) (Figure 1).

Table 1 displays the frequency of SIBO detection by the etiology of cirrhosis, in addition to the main characteristics of the 50 participants with cirrhosis. The only etiology in which SIBO was detected significantly less often than the other etiologies was cirrhosis caused by autoimmune hepatitis (2 of 11 vs. 24 of 39; p=0.016).

Table 3. Comparison of the main hemodynamic parameters (mean±standard deviation) in 15 healthy people (Group H), people with cirrhosis with SIBO (C-SIBO[+]), and people with cirrhosis without SIBO (C-SIBO[-]).

	C-SIBO(+) group (n=26)	C-SIBO(-) group (n=24)	H group (n=15)	p, C-SIBO(+) group vs. C-SIBO (-) group	p, H group vs. C-SIBO group (+)	p, H group vs. C-SIBO group(-)
Mean pulmonary arterial pressure, mmHg	20.4±5.8	18.1±6.4	15.1±2.5	0.220	0.003	0.175
Early ventricular filling velocity (E), m/s	0.84±0.21	0.79±0.29	0.72±0.14	0.166	0.101	0.919
Late ventricular filling velocity (A), m/s	0.72±0.18	0.76±0.22	0.54±0.08	0.481	0.003	0.001
End-diastolic volume, mL	120.9±28.7	99.9±22.0	94.9±15.3	0.005	0.003	0.583
End-systolic volume, mL	46.7±12.5	38.4±8.3	33.7±7.0	0.009	0.001	0.083
Ejection fraction, %	61.5±4.0	61.4±3.5	64.7±2.8	0.961	0.004	0.004
Left ventricular mass index, g/m^2	161.4±41.2	142.7±35.0	116.5±21.5	0.220	<0.001	0.095
Stroke volume, mL	74.2±18.0	61.5±14.8	61.3±9.3	0.009	0.010	0.931
Heart rate, bpm	73.1±11.5	74.1±9.4	72.1±6.0	0.651	0.914	0.544
Cardiac output, L/min	5.38±1.41	4.52±1.03	4.40±0.68	0.034	0.041	0.795
Systolic blood pressure, mmHg	110.2±12.3	126.2±21.0	121.2±9.8	0.005	0.011	0.554
Diastolic blood pressure, mmHg	69.0±8.7	74.9±12.3	72.7±5.65	0.040	0.120	0.403
Mean arterial pressure, mmHg	82.7±9.0	92.0±14.0	88.8±5.8	0.016	0.032	0.402
Systemic vascular resistance, dyn·s·cm^{-5}	1312±352	1704±424	1648±272	0.001	0.006	0.874
Pulse pressure, mmHg	41.2±9.5	51.3±15.3	48.5±9.4	0.020	0.034	0.851
Total arterial compliance, mL/mmHg	1.87±0.57	1.27±0.37	1.29±0.26	<0.001	<0.001	0.554

Significant differences are marked in bold italics.

Table 3 displays the main hemodynamic parameters observed in healthy controls (Group H), in people with SIBO and without SIBO, and comparisons among these groups.

The mean pulmonary artery pressure and left ventricular mass index were significantly greater in C-SIBO(+) than in controls, but not when compared with C-SIBO(-). There was no significant difference in these parameters between the C-SIBO(-) group and the control group.

Late ventricular filling velocity (A) was significantly greater in people with cirrhosis compared with controls. However, this difference was not significant between the C-SIBO(+) and C-SIBO(-) groups. There was no significant difference in early ventricular filling velocity (E) among the groups.

The end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and total arterial compliance were significantly greater in the C-SIBO(+) group, but not in the C-SIBO(-) group. Blood pressure and systemic vascular resistance were significantly lower in the C-SIBO(+) group, but not in the C-SIBO(-) group.

Ejection fraction in cirrhosis was slightly lesser, irrespective of the SIBO presence.

There was no significant difference in the heart rate between the groups. As shown in Table 4, total arterial compliance and pulse pressure in all participants with cirrhosis were the only hemodynamic parameters that differed between the groups CC-SIBO(+) and CC-SIBO(-). When comparing participants with decompensated cirrhosis, the end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and total arterial compliance were significantly greater while systolic, diastolic, and mean arterial pressure, and systemic vascular resistance were significantly smaller in the DC-SIBO(+) group than the DC-SIBO(-) group (Table 4).

There were no differences in hemodynamic parameters between participants with decompensated cirrhosis and participants with compensated cirrhosis among those with cirrhosis without SIBO. Among people with cirrhosis and with SIBO, participants with decompensated cirrhosis had a significant increase in the end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and mean pulmonary artery pressure, and a significant decrease in the systemic vascular resistance compared to participants with compensated cirrhosis (Table 4).

None of the participants had systolic heart failure as determined by echocardiography (ejection fraction <52% in males or <54% in females [16]).

Systemic vascular resistance was the only hemodynamic parameter that significantly correlated with the mean arterial pressure ($r=0.526$, $p<0.001$) in participants with cirrhosis. No hemodynamic parameter significantly correlated with the mean arterial pressure in the control group.

The CRP value was greater in the C-SIBO(+) group compared to the C-SIBO(-) group (10.5 mg/L [1.2-16.5] vs. 2.8 mg/L [0.6-9.1]; $p=0.028$), both in participants with compensated cirrhosis (4.5 mg/L [1.2-9.8] vs. 1.5 mg/L [0.1-1.9]; $p=0.028$) and in participants with decompensated cirrhosis (16.0 mg/L [5.3-22.5] vs. 8.7 mg/L [1.5-9.5]; $p=0.048$).

Among participants with cirrhosis, there was a statistically significant positive correlation between the CRP elevation and end-diastolic volume ($r=0.385$; $p=0.006$), end-systolic volume ($r=0.382$; $p=0.005$), left ventricle mass index ($r=0.412$; $p=0.004$), stroke volume ($r=0.354$; $p=0.012$), cardiac output ($r=0.313$; $p=0.027$), and total arterial compliance ($r=0.393$; $p=0.005$). In these same participants, there was a statistically significant negative correlation between the CRP elevation and systemic vascular resistance ($r=-0.367$; $p=0.009$). There was no significant correlation between the CRP and mean pulmonary artery pressure ($r=0.204$; $p=0.155$), heart rate ($r=-0.046$; $p=0.753$), ejection fraction ($r=-0.001$; $p=0.994$), systolic blood pressure ($r=-0.232$; $p=0.105$), diastolic blood pressure ($r=-0.260$; $p=0.068$), pulse pressure ($r=-0.165$; $p=0.252$), and mean arterial pressure values ($r=-0.227$; $p=0.113$).

Systemic inflammatory response, defined as CRP higher than 10 mg/L (23), was detected in 14 (53.8%) of the 26 participants from the C-SIBO(+) group and 2 (8.3%) of the 24 participants from the C-SIBO(-) group ($p=0.001$). When broken into subgroups, 12 (75.0%) of the 16 participants from the DC-SIBO(+) and 2 (13.3%) of the 15 participants from DC-SIBO(-) groups ($p=0.001$), 2 (20%) of the 10 from the CC-SIBO(+) group, and no participants from the CC-SIBO(-) group ($p=0.474$) had systemic inflammatory response.

Participants with cirrhosis with SIBO had significantly higher rates of hyperdynamic circulation (cardiac output >5.5 L/min) and vasodilatation (systemic vascular resis-

Table 4. SIBO and the main hemodynamic parameters (Mean±Standard Deviation) in participants with compensated and decompensated cirrhosis.

	Compensated Cirrhosis (n=19)			Decompensated Cirrhosis (n=31)		
	CC-SIBO(+) Group (n=10)	CC-SIBO(-) Group (n=9)	p	DC-SIBO(+) Group (n=16)	DC-SIBO(-) Group (n=15)	p
Mean pulmonary artery pressure, mmHg	16.8±4.2	16.8±5.0	0.780	22.7±5.5	18.9±7.2	0.086
End-diastolic volume, mL	102.00±15.62	97.44±17.38	0.661	132.75±29.02	101.47±24.86	0.002
End-systolic volume, mL	40.20±6.39	38.22±7.31	0.447	50.75±13.85	38.53±9.02	0.008
Ejection fraction, %	60.54±3.23	60.74±3.11	0.968	62.03±4.48	61.77±3.77	0.953
Left ventricular mass index, g/m^2	149.56±33.14	139.71±30.06	0.842	168.76±45.00	144.78±39.05	0.232
Heart rate, bpm	70.80±12.74	71.89±9.37	0.842	74.56±10.79	75.47±9.48	0.830
Stroke volume, mL	61.80±10.62	59.22±10.97	0.719	82.00±17.51	62.93±16.85	0.005
Cardiac output, L/min	4.31±0.67	4.27±1.01	0.905	6.06±1.34	4.67±1.04	0.002
Systolic blood pressure, mmHg	110.60±12.67	123.67±16.09	0.079	109.94±12.49	127.67±23.96	0.041
Diastolic blood pressure, mmHg	70.5+6.3	70.7+15.5	0.719	68.00±9.99	77.47±9.65	0.017
Mean arterial pressure, mmHg	83.87±7.10	88.33±14.92	0.604	81.98±10.17	94.20±13.50	0.012
Pulse pressure, mmHg	40.1±11.5	50.3±10.4	0.010	41.9±8.3	50.2±17.9	0.446
Systemic vascular resistance, dyn·s·cm^{-5}	1589±252	1748±505	0.400	1133±287	1675±386	<0.001
Total arterial compliance, mL/mmHg	1.61±0.38	1.16±0.36	0.006	2.04±0.62	1.33±0.38	0.001
	C-SIBO(+) (n=26)			C-SIBO(-) (n=24)		
	DC-SIBO(+) (n=16)	CC-SIBO(+) (n=10)	p	DC-SIBO(-) (n=15)	CC-SIBO(-) (n=9)	p
Mean pulmonary artery pressure, mmHg	22.7±5.5	16.8±4.2	0.007	18.9±7.2	16.8±5.0	0.726
End-diastolic volume, mL	132.75±29.02	102.00±15.62	0.001	101.47±24.86	97.44±17.38	0.861
End-systolic volume, mL	50.75±13.85	40.20±6.39	0.036	38.53±9.02	38.22±7.31	0.953
Ejection fraction, %	62.03±4.48	60.54±3.23	0.286	61.77±3.77	60.74±3.11	0.599
Left ventricular mass index, g/m2	168.76±45.00	149.56±33.14	0.262	144.78±39.05	139.71±30.06	0.844
Heart rate, bpm	74.56±10.79	70.80±12.74	0.484	75.47±9.48	71.89±9.37	0.482
Stroke volume, mL	82.00±17.51	61.80±10.62	0.001	62.93±16.85	59.22±10.97	0.640
Cardiac output, l/min	6.06±1.34	4.31±0.67	0.002	4.67±1.04	4.27±1.01	0.411
Systolic blood pressure, mmHg	109.94±12.49	110.60±12.67	0.897	127.67±23.96	123.67±16.09	0.907
Diastolic blood pressure, mmHg	68.00±9.99	70.50±6.26	0.698	77.47±9.65	70.67±15.51	0.174
Mean arterial pressure, mmHg	81.98±10.17	83.87±7.10	0.856	94.20±13.50	88.33±14.92	0.318
Pulse pressure, mmHg	41.9±8.3	40.1±11.5	0.484	50.2±17.9	53.0±10.4	0.446
Systemic vascular resistance, dyn·s·cm^{-5}	1133±287	1589±252	<0.001	1675±386	1748±505	0.596
Total arterial compliance, ml/mmHg	2.04±0.62	1.61±0.38	0.041	1.33±0.38	1.16±0.36	0.084

SIBO: small intestinal bacterial overgrowth; CC-SIBO(+): compensated cirrhosis with SIBO; CC-SIBO(-): compensated cirrhosis without SIBO; DC-SIBO(+): decompensated cirrhosis with SIBO; DC-SIBO(-): decompensated cirrhosis without SIBO.
Significant differences are marked in bold and italics.

Table 5. Frequency of hemodynamic changes and left ventricular hypertrophy in participants with cirrhosis by severity of cirrhosis and presence of SIBO.

Hemodynamic change		C-SIBO(+) Group (n=26)	C-SIBO(-) Group (n=24)	DC-SIBO(+) Group (n=16)	DC-SIBO(-) Group (n=15)	CC-SIBO(+) Group (n=10)	CC-SIBO(-) Group (n=9)
Hyperdynamic circulation	Present	13	5	12	4	1	1
	Absent	13	19	4	11	9	8
	p	0.042		0.012		1.000	
Vasodilatation	Present	10	2	10	1	0	1
	Absent	16	22	6	14	10	8
	p	0.020		0.002		0.474	
Left ventricular hypertrophy	Present	9	4	6	2	3	2
	Absent	17	20	10	13	7	7
	p	0.203		0.220		1.000	
Pulmonary hypertension	Present	7	3	6	3	1	0
	Absent	19	21	10	12	9	9
	p	0.294		0.433		1.000	

SIBO: small intestinal bacterial overgrowth; CC-SIBO(+): compensated cirrhosis with SIBO; CC-SIBO(-): compensated cirrhosis without SIBO; DC-SIBO(+): decompensated cirrhosis with SIBO; DC-SIBO(-): decompensated cirrhosis without SIBO; C-SIBO(+): cirrhosis with SIBO; C-SIBO(-): cirrhosis without SIBO. Significant differences are marked in bold and italics.

tance <1200 dyn·s·cm^{-5}) compared to people with cirrhosis without SIBO. This was true among participants with decompensated cirrhosis, but it was not true among participants with compensated cirrhosis. The rates of left ventricular hypertrophy (left ventricle mass index >95 g/m^2 for women or >115 g/m^2 for men [16]) and pulmonary hypertension (mean pulmonary artery pressure >25 mmHg at rest [24]) did not differ significantly between participants with and without SIBO (Table 5).

People with cirrhosis with vasodilatation, hyperdynamic circulation, hypotension, and left ventricular hypertrophy had higher CRP levels compared to people with cirrhosis without those hemodynamic changes (Figure 2). CRP levels tended to be greater in people who had cirrhosis with pulmonary hypertension (11.6 mg/L [0.4-19.9] vs. 6.0 mg/L [1.1-10.1]; p=0.389).

DISCUSSION

Our findings show that the hemodynamic changes in cirrhosis can be divided into three groups.

The first group consists of changes not associated with SIBO, such as a slightly decreased systolic function and diastolic dysfunction. These changes have previously been described as cirrhotic cardiomyopathy (25). They are found both in people with SIBO and in people without SIBO, and there is no difference between them. This allows us to conclude that SIBO does not seem to impact these hemodynamic parameters.

The second group consists of changes partly associated with SIBO. These are pulmonary hypertension and left ventricular hypertrophy. According to our findings, the mean pulmonary artery pressure and left ventricular mass index differ between people with cirrhosis with SIBO and healthy people, but they do not differ between people with cirrhosis with SIBO and without SIBO, and between people with cirrhosis without SIBO and healthy people.

The third group consists of changes that are strongly associated with SIBO. These are a decreased total arterial compliance, hyperdynamic circulation, vasodilatation, and hypotension. According to our findings, these changes present only in people with cirrhosis with SIBO. Total arterial compliance, cardiac output, systemic vascular resistance, and blood pressure differ between people with cirrhosis with SIBO and without SIBO, and between peo-

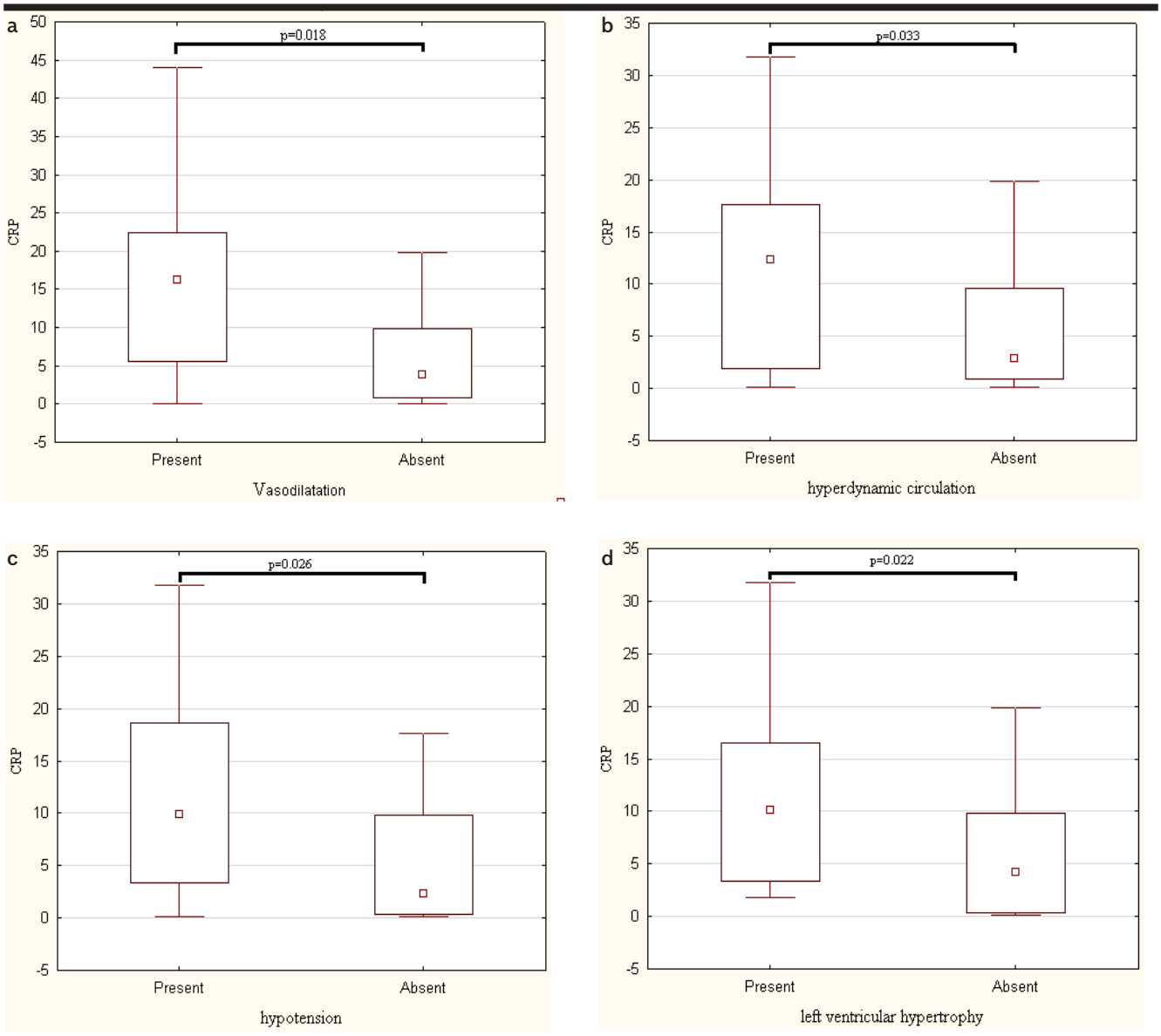

Figure 2. a-d. *CRP (mg/l) in people with cirrhosis with certain hemodynamic changes and in people with cirrhosis without these changes. The point in the box represents the median. The length of the box represents the interquartile range. The error bars show the non-outlier range. (a) Vasodilatation; (b) hyperdynamic circulation; (c) hypotension; (d) left ventricular hypertrophy.*

ple with cirrhosis with SIBO and healthy people, but they do not differ (p>0.900) between people with cirrhosis without SIBO and healthy people.

No systolic heart failure or changes in the heart rate in participants with cirrhosis occurred in the study.

According to our findings, SIBO is associated with hemodynamic changes in decompensated, but not in compensated cirrhosis.

Our study reveals that systemic vascular resistance is the main factor determining blood pressure in people with cirrhosis, but not in healthy people.

We hypothesize the following pathogenetic model of hyperdynamic circulation in cirrhosis based on the findings of this study and previously published data.

In compensated cirrhosis, the barrier functions of the gut and liver are preserved, and SIBO contributes mild bacte-

rial translocation with subsequent mild systemic inflammation. Tumor necrosis factor alpha (TNFa), a proinflammatory cytokine, reduces the tone of the smooth muscle of blood vessels through the activation of NO synthesis and other ways (6; 26). The smooth muscle of the large arteries determines total arterial compliance, and it is probably more sensitive to TNFa than the smooth muscle of the small arteries, which determines total arterial compliance. Thus, the tone of the former decreases enough to increase total arterial compliance and cause a decrease in pulse pressure. At the same time, the tone of the latter does not change significantly, so the systemic vascular resistance and mean arterial pressure remain practically unchanged, and activation of the systems regulating blood pressure does not occur.

In contrast, in decompensated cirrhosis, the barrier functions of the gut and liver fail, and SIBO contributes to moderate to severe bacterial translocation with subsequent moderate to severe systemic inflammation. The tone of the small arteries diminishes enough to decrease systemic vascular resistance and causes a drop in the mean arterial pressure. Significant decreases in the mean arterial pressure activate sympathoadrenal and the renin-angiotensin-aldosterone system (27). It is believed that the cardiotropic and vasoconstrictive action of these systems is blocked at the receptor and post-receptor levels by proinflammatory cytokines (25-26). The systemic vascular resistance remains decreased, and the heart rate does not increase, but water and sodium are retained. Water and sodium retention increases the total blood volume and venous return, which in turn cause an increased heart rate and ejection fraction in a healthy person through sympathoadrenal activation (the Bainbridge reflex). However, in a person with cirrhosis, the cardiotropic effect of the sympathoadrenal system is blocked, and an increased venous return causes an increase in end-diastolic volume that at fixed ejection fraction causes stroke volume and end-systolic volume to also increase (25). An increased stroke volume at a fixed heart rate leads to increased cardiac output, which in turn increases blood pressure, but not enough to normalize it. An increased cardiac output and increased venous return leads to increased pulmonary blood flow and pulmonary hypertension. Hyperdynamic circulation increases the work of the heart, which leads to left ventricular hypertrophy (28).

Hyperdynamic circulation increases portal blood inflow, worsening portal hypertension (28). Portal hypertension causes portal enteropathy and portosystemic blood bypass, worsening the barrier functions of the gut and liver, leading to a more intense bacterial translocation with a more severe systemic inflammation (6). The vicious circle completes quickly.

There is no gold standard for determining SIBO. The jejunal aspirate culture has been considered a gold standard for decades, but the North American Consensus from 2017 recommended the use of glucose or lactulose breath tests to diagnose SIBO because authors of the Consensus believed that these tests had less limitations (15).

We used a hydrogen breathing test with lactulose in accordance with these recommendations, although this test also has certain drawbacks. The development of reliable methods for detection of SIBO is an important task for future research.

Since, in our study, the use of proton pomp inhibitors was not associated with the risk of developing SIBO (10/16 vs. 9/15; p=1.000) in cirrhosis, we did not consider it as an exclusion criterion and a limitation of the study. In another larger study (9), it was also shown that the use of proton pomp inhibitors did not increase the risk of developing SIBO in cirrhosis.

The strength of our manuscript is that, to the best of our knowledge, we are the first who have comprehensively analyzed the association among SIBO, systemic inflammation, and hemodynamic changes in compensated and decompensated cirrhosis in a standardized cohort of study participants. Our findings allowed the division of hemodynamic changes in cirrhosis into three groups, as indicated above, according to the association with SIBO, and allowed us to suggest the pathogenesis of the development of the second- and third group changes.

Thus, in this small pilot study, we could confirm our hypothesis that SIBO is associated with hemodynamic parameters, causing systemic inflammation in cirrhosis without the development of an evident infection. However, the findings in our pilot study should be tested further in larger studies.

Another limitation of our study is using indirect measurements of hemodynamic parameters and the absence of invasive measurements of these parameters.

The limitations to our study are that it was an observational study and that we did not have the opportunity to measure any marker of bacterial translocation (bacterial

DNA and others) and proinflammatory cytokines (TNFa and others). Further studies measuring these indicators are required to evaluate the correctness of the proposed hypothesis. Further studies are also required to determine how eradication of SIBO (using antibiotics, probiotics, or prokinetics) may impact on bacterial translocation, hemodynamic changes, and portal hypertension in cirrhosis. Kimer and colleagues and Rasaratnam and colleagues have investigated the effect of antibiotics on the hemodynamics in decompensated cirrhosis (29-30). Their results were contradictory. In their studies, SIBO was not determined, and the difference in the percent of people with SIBO may explain the different results.

In conclusion, SIBO seems to be associated with hyperdynamic circulation in cirrhosis and may be a principal factor that causes it through systemic inflammation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - V.I.; Design - C.P.; Supervision - R.M.; Resources - C.P.; Materials - R.M.; Data Collection and/or Processing - R.M.; Analysis and/or Interpretation - V.I.; Literature Search - V.I.; Writing Manuscript - R.M.; Critical Review - V.I., C.P.

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