Reduced baroreflex sensitivity in alcoholic cirrhosis: relations to hemodynamics and humoral systems

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Møller S, Iversen JS, Henriksen JH, Bendtsen F. Reduced baroreflex sensitivity in alcoholic cirrhosis: relations to hemodynamics and humoral systems. Am J Physiol Heart Circ Physiol 292: H2966–H2972, 2007. First published February 9, 2007; doi:10.1152/ajpheart.01227.2006.—In cirrhosis, arterial vasodilatation leads to central hypovolemia and activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. As the liver disease and circulatory dysfunction may affect baroreflex sensitivity (BRS), we assessed BRS in a large group of patients with cirrhosis and in controls who were all supine and some after 60° passive head-up and 30° head-down tilting in relation to central hemodynamics and activity of the sympathetic nervous and renin-angiotensin-aldosterone systems. One-hundred and five patients, aged 58.6 yr (SD 11.7), without liver disease, who were referred for a hemodynamic investigation to exclude circulatory disorders, including one hundred and five patients eligible for the study underwent a tilting procedure after having given their informed and signed consent, in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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CIRRHOSIS IS ASSOCIATED WITH A splanchnic arterial vasodilatation that leads to a hyperdynamic circulation with augmented cardiac output (CO) and heart rate (HR) and reduced arterial blood pressure (28, 37, 41). In patients with advanced disease, the central blood volume (CBV) is displaced to peripheral and splanchnic vascular territories with central hypovolemia and activated counterregulatory mechanisms, such as the sympathetic nervous (SNS) and the renin-angiotensin-aldosterone systems (RAAS), as the outcome (6, 28, 36). At the upright position, arterial, central venous, and pulse pressures fall, and there is a close relation between the decline in pulse pressure on the one hand and the rising HR and declining splanchnic blood flow on the other, which suggests that arterial baroreceptors initiate the increase in HR and splanchnic vasoconstriction (34). A cardiovascular autonomic dysfunction is well established in cirrhosis of different etiologies (13, 15), and impaired baroreflex sensitivity (BRS) has been suggested (1, 18, 30, 39). An alcoholic etiology may aggravate the cardiovascular changes induced by cirrhosis, although several studies have reported no differences in the severity of neuropathy relating to cause (2, 5). As liver and cardiovascular dysfunctions individually may affect the baroreceptor function in cirrhosis, the aims of the present study were to assess BRS in a large group of patients and in matched controls in relation to severity of liver disease and central hemodynamics and, moreover, to analyze the effects of passive tilting on BRS.

MATERIALS AND METHODS

One-hundred and five consecutive patients, aged 54.9 yr (SD 9.1) (37 women and 68 men), with verified alcoholic cirrhosis were entered in the study. All of the patients had abstained from alcohol for at least 2 mo before the study. The diagnosis was based on liver biopsy and accepted clinical and biochemical criteria of cirrhosis. Patients were stratified according to the modified Child-Turcotte class A, 55 to Child class B, and 29 to Child class C. Fifty-five patients had ascites confirmed by ultrasonography. Diuretics were stopped 24 h before the study. No patients had hepatorenal syndrome or evidence of subacute bacterial peritonitis. None of the patients was taking cardiovascular medication, including β-blockers and calcium channel blockers. At endoscopy, 71 patients had esophageal varices. None of the patients had hepatic encephalopathy or had experienced recent gastrointestinal bleeding. A matched control group consisted of 11 individuals (5 women and 6 men), aged 58.6 yr (SD 11.7), without liver disease, who were referred for a hemodynamic investigation to exclude circulatory disorders, mainly intestinal ischemia, which were not found. None of the controls received any cardiac medication. The first consecutive 23 cirrhotic patients eligible for the study underwent a tilting procedure as described later. For this part of the study, 14 other healthy volunteers (8 women and 6 men) with no known disease served as a control group; none was taking medication. Patients and controls participated after giving their informed and signed consent, in accordance with the Helsinki II Declaration, and the study was approved by the local Ethics Committee for Medical Research in Copenhagen (journal no. KF 01-294/99). No complications or side effects were encountered during the study. Clinical, biochemical, and hemodynamic characteristics of the patient and control groups are shown in Table 1.

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Hemodynamic investigations. Patients and controls underwent a hemodynamic investigation in the morning after an overnight fast and at least 1 h resting in the supine position. Hepatic veins and femoral arteries were catheterized as described elsewhere (26). The hepatic venous pressure gradient was determined as the wedged minus free hepatic vein pressures. Mean arterial pressure (MAP) was determined by electronic integration of the pressure signal. CO was measured by the indicator dilution method, as previously described (26). Systemic vascular resistance (SVR), expressed in dyn·s·cm⁻⁵, was assessed as 80 × (MAP − RAP/CO), where RAP is right atrial pressure; pressures were expressed in mmHg and CO in l/min. HR was determined by ECG. The central circulation time (CCT), representing the mean indicator sojourn in the CBV and the CBV itself, were both assessed in accordance with the kinetic theory, as described earlier (26, 28).

Measurement of BRS. Information on the source of variability of blood pressure and the RR interval can be obtained by spectral analysis. The total spectrum can be divided into three bands: low frequency (0.02–0.06 Hz), midfrequency (0.07–0.14 Hz), and high frequency (0.15–0.40 Hz). The slow variations are related to respiratory activity and are mainly of parasympathetic origin (32). The modulus (gain) function specifies the ratio between changes in RR interval time and changes in systolic blood pressure values attributable to respiratory activity and are mainly of parasympathetic origin (32). The modulus in the midfrequency band reflects the function of the blood pressure control system. The dynamic baroreflex gain can be divided into three spectral bands: low frequency (0.04 Hz), midfrequency (0.1 Hz), and high frequency (0.25 Hz). Variations in the midfrequency band are believed to originate from the characteristics of the blood pressure control system.

Ganz catheter was inserted into the right atrium of a subset of 23 cirrhotic patients and controls, and baseline measurements of CO, SVR, CBV, and CCT were taken after 1 h in the supine position. Blood samples for norepinephrine, renin, and aldosterone were taken from the femoral artery. Patients and controls were then laid in a 30° head-down position (Trendelenburg’s position) for 20 min, while the determination of arterial blood pressures, RAP, CO, SVR, CBV, CCT,
and neurohumoral substances was repeated. After the 20-min head-down, the subjects reassumed the supine position. They were then moved to a tilting table and passively erected to a 60° head-up position. The time supine was not less than 20 min to ensure the steady state. All measurements were repeated after 20 min of tilting or at the time of complaints of dizziness. The time from the start of the period to complaints of dizziness was recorded, and in the case of discomfort the patient was returned to the supine position. Our laboratory has previously, in part, reported effects of passive tilting on CO, CCT, CBV, MAP, HR, serum renin, aldosterone, and norepinephrine in the 23 patients (29).

**Assays.** The serum concentrations of liver function tests were determined by routine methods. Plasma concentrations of norepinephrine were determined by HPLC, as described elsewhere (25). The circulating plasma renin and aldosterone concentrations were determined with commercially available kits, as reported elsewhere (29).

Data are presented as means (SD). Vasoactive substances and BRS data are additionally shown as medians and total ranges due to a nonnormal distribution. Statistical analyses were performed by unpaired Student’s t-test or the Mann-Whitney test and paired Student’s t-test or the Wilcoxon test, as appropriate. Correlation analyses between independent variables were performed by the Spearman’s rank correlation test. A backward stepwise multiple-regression analysis was used to determine independent physiological correlates to BRS. A P value <5% was considered significant.

**RESULTS**

Patients and controls were matched anthropometrically (Table 1). Patients with cirrhosis had significant portal hypertension [hepatic venous pressure gradient: 15 mmHg (SD 6)] and impaired liver function with ascsites in 55 patients (Table 1). The HR was higher in the total patient population than in the controls, 78 (SD 14) vs. 70 min⁻¹ (SD 9), P < 0.001, and the plasma volume was expanded in the patients, 54.8 (SD 9.3) vs. 44.5 ml/kg (SD 5.0), P < 0.001. In the cirrhotic patients who underwent tilting, 2 patients belonged to Child class A, 13 to Child class B, and 8 to Child class C. These patients were not significantly different from the total patient population with respect to hemodynamics and hepatic functional characteristics. At baseline, they had a hyperdynamic circulation with increased CO, 8.1 (SD 2.1) vs. 6.8 l/min (SD 1.4), P < 0.05, and increased HR, 84 (SD 11) vs. 65 min⁻¹ (SD 8), P < 0.001, but their systolic blood pressures did not differ significantly from that of the controls, 135 (SD 21) vs. 131 mmHg (SD 16) (not significant).

In the total patient population, the median BRS was significantly lower in the cirrhotic patients, 3.7 (range 0.3–30.7) ms/mmHg, than in the matched controls, 14.3 (6.1–23.6) ms/mmHg, P < 0.001. The BRS in the individual Child groups is shown in Fig. 2. BRS was significantly lower in Child class A patients (P < 0.01) and Child class B and C patients compared with controls (P < 0.001). In the total patient group, there were no significant differences in BRS with respect to gender, presence of ascites, or esophageal varices.

In the total patient population, BRS correlated significantly with blood hemoglobin, serum sodium, the Child score, HR, CCT, arterial CO₂ tension, and arterial pH (Table 2). In a backward stepwise multiple-regression analysis, serum sodium (P = 0.044), HR (P = 0.027), and CCT (P = 0.034) were the best independent physiological correlate to BRS (Table 3). Patients with a blood hemoglobin concentration higher than the median level of 7.4 mmol/l had a higher BRS, 6.4 ms/mmHg, than those with a lower than median hemoglobin concentration, 4.5 ms/mmHg (P < 0.01).

Figure 3 shows results of BRS, blood pressure, and HR in the patients and controls at baseline, after 30° head-down tilting, and after 60° head-up tilting. Like in the total group of cirrhotic patients, BRS was significantly lower in these patients than in the controls at baseline (P < 0.02) and during the head-down tilt (P < 0.03). However, after head-up tilting, BRS changed in both cirrhotic patients and controls by −37 and −62%, respectively (not significant), and there was now no difference in BRS in this position (Fig. 3). CCT was significantly shorter in the patients than in the controls at baseline, 10.2 (SD 1.9) vs. 12.6 s (SD 1.8) (P < 0.001); it increased by 30% after head-up tilting in the cirrhotic patients (P < 0.001), whereas there was no significant difference in the controls. CO decreased by −36 and −35%, respectively (not significant), and no significant difference between the groups remained. BRS in the cirrhotic patients correlated directly with CCT at baseline (r = 0.68, P = 0.001), but not after tilting.

After head-up tilting, norepinephrine increased from 681 (237–1,506) pg/ml to 980 (461–2,353) pg/ml in the cirrhotic patients (P < 0.001) and from 319 (176–585) pg/ml to 525 (238–718) pg/ml in the controls (P < 0.001). Plasma renin increased from 38 (5–2,850) pg/ml to 89 (5–7,200) pg/ml in the cirrhotic patients (P < 0.002) and was unaltered in the controls: 7 (5–17) pg/ml vs. 8 (5–26) pg/ml. Plasma aldosterone changed from 249 (68–4,440) pmol/l to 628 (106–4,440) pmol/l (P < 0.001) in the cirrhotic patients and from 229 (88–415) pmol/l to 370 (172–898) pmol/l (P < 0.001) in the controls. Head-down tilting did not significantly change baseline values in any of the hormone systems, neither in the cirrhotic patients nor in the controls. At baseline, BRS correlated negatively with plasma renin (r = −0.60, P = 0.007) and serum aldosterone (r = −0.45, P = 0.05), but not to circulating norepinephrine (Fig. 4). Elimination of the two outliers did not significantly change the correlation coefficients.

**DISCUSSION**

In this study, we hypothesized that BRS in cirrhosis is affected by the presence of hepatic and cardiovascular dysfunction and may change with posture. The main findings of
our study are that 1) BRS is reduced in patients with cirrhosis in relation to the severity of the liver dysfunction; 2) the reduced BRS in cirrhosis is related to determinants of the hyperdynamic circulation and the filling of the central circulation; 3) head-up tilting attenuates the hyperdynamic circulation in advanced cirrhosis and gives no further reduction in BRS, but affects the CCT differentially in patients and controls; and 4) plasma renin, aldosterone, and norepinephrine are all increased at baseline, and the RAAS correlates with BRS and increases further in patients with cirrhosis after head-up tilting.

Baroreceptors are an integral part of the regulatory system involved in the maintenance of circulatory stability. Reaction of the high-pressure arterial baroreceptors to a fall in arterial blood pressure brings about a decrease in the tonic inhibitory traffic to the central nervous system, leading to a rise in efferent sympathetic activity, which will raise arterial vascular tone and activate other neurohumoral systems to help preserve cardiovascular stability (14, 34). A decrease in cardiac preload or arterial pressure inhibits baroreceptor activity and results in a simultaneous activation of the vasoconstrictor systems: the SNS and the RAAS (3, 14). Several studies have shown a general autonomic dysfunction in cirrhosis with impairment of both sympathetic and parasympathetic reflexes (20) and relations to the degree of hepatic dysfunction and mortality (15).

The site of the autonomic dysfunction and the vascular hyporeactivity in cirrhosis is under debate, but may originate within the central nervous system, the autonomic nervous system, or from local mediators or within the smooth muscle cells (27). The BRS was reduced in the supine patients. This means that, in the case of the low arterial blood pressure often seen in cirrhosis, the circulatory adaptation, for example, to pressor stimuli is reduced (35). This may contribute substantially to the vascular hyporeactivity described in experimental and clinical cirrhosis (4, 22). The inverse relation between BRS and the RAAS in the supine position suggests that this system in particular could be involved in the reduced BRS. In the erect position, there were no significant correlations between BRS and RAAS or norepinephrine.

BRS may be assessed by various methods, such as Valsalva’s maneuver, head-up tilting, lower body negative pressure application (neck suction), and intravenous bolus injection of vasoactive agents without direct effects on the heart (e.g., phenylephrine) (31). Data are usually derived from measurements in the time domain or in the frequency domain, and the correlation between the different methods may vary (9, 32). This is, however, to be expected, owing to the marked differences in the assumptions between the two methodologies (9). In this respect, it is important to be aware that the different methods of estimating baroreflex function are complementary and not mutually excluding. In studies of a small number of patients with cirrhosis, BRS has been assessed by various methods, which have given somewhat discrepant results, as BRS has been found to be reduced (1, 39) or normal (19). The methods applied may, to a certain degree, explain the variation

| Table 2. Correlations between the BRS and pertinent clinical and biochemical characteristics of 105 patients with cirrhosis |
|-----------------|-----------------|-----------------|
|                  | BRS             |                  |
|                  | Coefficient (r) | P Value         |
| Blood hemoglobin, mmol | 0.26 | 0.008           |
| Serum sodium, mmol/l | 0.29 | 0.003           |
| Child score       | −0.25 | 0.01            |
| Heart rate, beats/min | −0.51 | 0.0001         |
| Central circulation time, s | 0.41 | 0.0001         |
| Central blood volume, liter | 0.18 | 0.06            |
| Arterial CO₂ tension, kPa | 0.29 | 0.004           |
| Arterial pH, units | −0.29 | 0.005           |

BRS, baroreflex sensitivity.

Table 3. Multiple-regression analysis of determinants of BRS in 105 patients with cirrhosis

<table>
<thead>
<tr>
<th>BRS vs. Variable</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>0.19</td>
<td>0.09</td>
<td>0.044</td>
</tr>
<tr>
<td>Heart rate</td>
<td>−0.11</td>
<td>−0.05</td>
<td>0.027</td>
</tr>
<tr>
<td>Central circulation time</td>
<td>0.52</td>
<td>0.25</td>
<td>0.034</td>
</tr>
<tr>
<td>Constant</td>
<td>−17.93</td>
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The r² for model = 0.25, P < 0.001.
in the results. Few studies have assessed BRS by the sequence or the spectral power analysis (18, 39). In some studies, BRS has been related to the degree of liver dysfunction, as reflected in the Child score (16, 39). This agrees with our results, as we found a comparable relation to the Child score, which emphasizes the dependency of the autonomic dysfunction on the severity of the liver disease. The direct relation between BRS and blood hemoglobin probably indicates that patients with anemia have a more advanced stage of disease, indicating that anemia should be considered a confounder in the evaluation of abnormal BRS. Another potential confounder could be differences in nutritional status, which, however, may be less likely in our patients, as we found a comparable lean body mass throughout the patient classes and controls.

According to the peripheral arterial vasodilatation hypothesis, a decreased SVR results in abnormal distribution of the blood volume with a reduced effective arterial blood pressure and thereby reduced CCT and baroreceptor-induced activation of the SNS and RAAS and the development of a hyperdynamic circulation, including increased HR (37). Our findings of an inverse correlation between BRS and the HR and a direct relation between BRS and the CCT, reflecting the reduced central vascular compartment, suggest that the baroreceptor dysfunction may be intimately implicated in the hemodynamic derangement in cirrhosis.

Autonomic and peripheral neuropathy is well known in patients with alcoholic cirrhosis, and, therefore, an influence of a potential alcoholic neuropathy on the cardiovascular response cannot be totally ruled out. However, the patients were all abstaining from alcohol before the study, which excludes an acute effect of alcohol on the results. Moreover, none of the patients exhibited signs, symptoms, or complaints of peripheral neuropathy, which makes an interference of alcoholic neuropathy less likely. Finally, previous comparable studies of autonomic function in cirrhosis found no differences in the severity of neuropathy relating to etiology of cirrhosis (2, 5). Laffi et al. (18) have previously assessed BRS by power spectral analysis after tilting in 15 cirrhotic patients. In this study, the authors found no significant differences in the BRS of patients and controls in the supine position, but after tilting they observed reduced BRS in the cirrhotic patients, pointing to a receptor or postreceptor defect of the autonomic impairment in cirrhosis (18). In contrast to this study, but in agreement with other studies using power spectral analysis (1, 39), we found reduced BRS in the supine position in cirrhosis and a further reduction in BRS during head-up tilt. This response was similar to that observed in the controls and agrees with previous studies that have reported a relation between a decreased arterial baroreflex modulus at high tilting angles (7). Among the reasons for these discrepancies may be the severity of the patients’ liver disease, the etiology of the disease, and the methods using low-frequency-to-high-frequency ratio, as discussed above. However, there is agreement that the BRS in the supine position and the hemodynamic response to tilting are impaired in patients with cirrhosis, depending on the severity of the disease. In the paper by Laffi et al. (18), the severity of the disease in their patients was comparable to that of our patients, but the etiology was primarily hepatitis B, whereas in our patients the etiology was primarily alcoholic. A hypothesis that can be derived from our study is that the low supine BRS in cirrhosis may not be a fixed, structural defect, as it is influenced by physiological maneuvers such as head-up tilting. This notion is supported by the finding of increased BRS after exercise in healthy middle-aged men (23). On the other hand, this fact could introduce a bias because of a better fitness, especially of the younger controls and the presence of comorbid factors and age-related effects in the patients.

Both the RAAS and the SNS, as reflected by the increased circulating renin and norepinephrine concentrations, were activated in patients with cirrhosis, and these increased further during 60° head-up tilting. Both systems are regulated through the activity of the baroreceptors. However, we were not able to find a significant relation between circulating plasma norepinephrine and BRS, but, in this setting, norepinephrine is a relatively insensitive marker of the sympathetic drive. Recently, however, Iga et al. (17) investigated autonomic nervous function by $^{123}$I-metaiodobenzylquandine myocardial scintigraphy, power spectral analysis, and circulating catecholamines and found that the washout rate of $^{123}$I-metaiodobenzylquandine, low-frequency-to-high-frequency ratio, and blood levels of norepinephrine increased with the progression of the cirrhosis. Moreover, the authors found a relation between BRS and serum albumin and coagulation factors, but not to catecholamines (17). The results of this study also point out that the site of the autonomic abnormalities may be the heart.

After tilting, the activated RAAS increased further, probably because of baroreceptor deactivation. In the subset of cirrhotic patients, both renin and aldosterone correlated significantly with BRS at baseline. From a theoretical point of view, increased renin and aldosterone release can be attributed to stimulation of a renal baroreceptor (8), as well as central arterial baroreceptors with increased renal sympathetic nervous activity, which would also increase renin release (12). Which

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Fig. 4. Correlation between BRS and circulating plasma renin ($r = -0.60, P < 0.007$) and plasma aldosterone ($r = -0.45, P < 0.05$). Elimination of the two outliers did not significantly change the correlation coefficients.
of these two mechanisms that may be responsible for the observed relation cannot be settled from this study. However, results in experimental cirrhosis suggest that the impaired baroreflex control of renal SNS activity contributes to the lack of normal hemodynamic regulation (33). Moreover, there is experimental and clinical evidence that components of the RAAS, such as angiotensin II and aldosterone, interfere with the baroreceptor response (12, 42, 43). Hence results of angiotensin II receptor blockade in rats indicate that increased activity of RAAS contributes to increased renal SNS activity and its abnormal arterial baroreflex regulation in cardiac failure (10, 11). Yee and Struthers (42) and Monahan et al. (24) found that aldosterone impaired both parasympathetic and sympathetic components of BRS. In healthy volunteers, blockade of endogenous angiotensin II improved baroreceptor function, and angiotensin I receptor antagonism and angiotensin I-converting enzyme inhibition appeared to be equally effective in restoring the baroreceptor function in salt-depleted normotensive subjects (43). In patients with cirrhosis, Villa et al. (40) found that an aldosterone antagonist normalized the cardiac response to postural challenge. Dillon and coworkers (13) had previously reported a correction of the autonomic dysfunction by captopril in patients with cirrhosis. Thus there is substantial evidence that the RAAS is deeply involved in the impaired baroreflex function in cirrhosis and that the system may be partly restored by blockade of this system (38).

In conclusion, our results demonstrate that the BRS is reduced in supine patients with cirrhosis relating to various aspects of liver dysfunction and circulatory dysfunction. Moreover, the reduced BRS is related to RAAS, which may contribute to the impaired baroreflex function. Taken together, our results indicate that compensatory mechanisms to vasodilatation may be involved in the low BRS in cirrhosis. The low BRS may contribute to dysregulation of blood pressure and poor cardiovascular adaptation to circulatory challenges.

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