Reduced baroreflex sensitivity and pulmonary dysfunction in alcoholic cirrhosis: effect of hyperoxia

Søren Møller,1 Jens S. Iversen,2 Aleksander Krag,3 Peter Bie,4 Andreas Kjær,5 and Flemming Bendtsen3
1Department of Clinical Physiology, Hvidovre Hospital, 2Department of Nephrology Herlev Hospital, and 3Department of Medical Gastroenterology, Hvidovre Hospital, Faculty of Health Sciences, University of Copenhagen; 4Department of Physiology and Pharmacology, University of Southern Denmark, Odense; and 5Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Submitted 25 February 2010; accepted in final form 30 June 2010

Møller S, Iversen JS, Krag A, Bie P, Kjær A, Bendtsen F. Reduced baroreflex sensitivity and pulmonary dysfunction in alcoholic cirrhosis: effect of hyperoxia. Am J Physiol Gastrointest Liver Physiol 299: G784–G790, 2010. First published July 8, 2010; doi:10.1152/ajpgi.00078.2010.—Patients with cirrhosis exhibit impaired regulation of the arterial blood pressure, reduced baroreflex sensitivity (BRS), and prolonged QT interval. In addition, a considerable number of patients have a pulmonary dysfunction with hypoxemia, impaired lung diffusing capacity (DLCO), and presence of hepatopulmonary syndrome (HPS). BRS is reduced at exposure to chronic hypoxia such as during sojourn in high altitudes. In this study, we assessed the relation of BRS to pulmonary dysfunction and cardiovascular characteristics and the effects of hyperoxia. Forty-three patients with cirrhosis and 12 healthy matched controls underwent hemodynamic and pulmonary investigations. BRS was assessed by cross-spectral analysis of variabilities between blood pressure and heart rate time series. A 100% oxygen test was performed with the assessment of arterial oxygen tensions (Pao2) and alveolar-arterial oxygen gradient. Baseline BRS was significantly reduced in the cirrhotic patients compared with the controls. The frequency-corrected QT interval was significantly prolonged in the cirrhotic patients. There was no significant difference in BRS according to presence of HPS, Pao2, DLCO, or Child-Turcotte score, but BRS correlated with metabolic and hemodynamic characteristics. After 100% oxygen inhalation, BRS and the QT interval remained unchanged in the cirrhotic patients. In conclusion, BRS is significantly reduced in patients with cirrhosis compared with controls, but it is unrelated to the degree of pulmonary dysfunction and portal hypertension. Acute hyperoxia does not significantly revert the low BRS or the prolonged QT interval in cirrhosis.

Address for reprint requests and other correspondence: S. Møller, Dept. of Clinical Physiology and Nuclear Medicine, 239, Hvidovre Hospital, DK-2650 Hvidovre, Denmark (e-mail: soeren.moeller@hvh.regionh.dk).

Reduced baroreflex sensitivity and pulmonary dysfunction in alcoholic cirrhosis is a basic part of an autonomic dysfunction that affects cardiovascular regulation in cirrhosis. Thus patients with advanced cirrhosis have cardiac dysfunction with prolonged QT interval and abnormal blood pressure regulation partly owing to reduced baroreflex sensitivity (BRS) and pulmonary dysfunction and portal hypertension. In healthy individuals, BRS is reduced at exposure to acute and chronic hypoxia such as during sojourn in or simulation of high altitudes. Moreover, BRS is reduced in patients with chronic obstructive pulmonary disease partly because of central effects of hypoxia. The present study was undertaken to assess the relation between the reduced BRS and pulmonary dysfunction and to study the effects of hyperoxia on BRS, QT interval, and neurohumoral regulatory systems in patients with cirrhosis and in healthy controls. We hypothesized that oxygen inhalation could fully or partly revert BRS and the neurohumoral changes in cirrhosis.

METHODS

Study Population

Forty-three patients aged 57.4 ± 9.1 yr (mean ± SD) yr (14 women and 29 men) were entered in the study. All patients had verified alcoholic cirrhosis, i.e., an alcohol consumption exceeding 50 g alcohol per day for more than 5 yr. All patients had abstained from alcohol for at least 2 mo before the study. Cirrhosis was diagnosed on liver biopsy in 30% of classical, accepted clinical and biochemical criteria and presence of portal hypertension. Patients were stratified according to the Child-Turcotte score, and additionally the MELD score (The Model for End-Stage Liver Disease) was calculated. Twenty-four patients had ascites confirmed by ultrasonography. Diuretics were stopped 24 h before the study. None of the patients were taking cardiovascular medication, neither beta-blockers nor calcium channel blockers. None of the patients had signs of infections or received antibiotics within 3 wk before the study or during the study period. An age-matched control group consisted of 12 volunteers (6 women and 6 men) aged 53.9 ± 8.4 yr without liver disease. None were taking medication. Twenty-four of the patients and seven controls were smokers. The patients and controls were instructed not to smoke 6 h prior to the investigations.

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 11-057/03). 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.
Table 1. Clinical, biochemical, and hemodynamic characteristics of 43 patients with cirrhosis and 12 controls

<table>
<thead>
<tr>
<th></th>
<th>Patients with Cirrhosis (n = 43)</th>
<th>Controls (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>29/14</td>
<td>6/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.4 ± 9.1</td>
<td>53.9 ± 4.8</td>
</tr>
<tr>
<td>Ascites, ±</td>
<td>19/24</td>
<td>(0/12)</td>
</tr>
<tr>
<td>Child class, A/B/C</td>
<td>17/18/8</td>
<td>n.a.</td>
</tr>
<tr>
<td>Child score</td>
<td>6.7 ± 2.0</td>
<td>n.a.</td>
</tr>
<tr>
<td>MELD Score</td>
<td>11.0 ± 2.6</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma coagulation factors II, VII, and X, units; 0.70–1.30</td>
<td>0.62 ± 0.18*</td>
<td>0.97 ± 0.27</td>
</tr>
<tr>
<td>Serum albumin, μmol/l; 540–800</td>
<td>520 ± 95*</td>
<td>557 ± 50</td>
</tr>
<tr>
<td>Serum bilirubin, μmol/l; 2–17</td>
<td>16 (4–69)*</td>
<td>7 (3–11)</td>
</tr>
<tr>
<td>Serum sodium, mmol/l; 136–146</td>
<td>139 ± 5</td>
<td>141 ± 3</td>
</tr>
<tr>
<td>Serum creatinine, mmol/l; &lt;120</td>
<td>84 ± 23</td>
<td>73 ± 13</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic venous pressure gradient, mmHg: &lt;5</td>
<td>15.3 ± 6.3</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Hepatic blood flow, l/min, 0.5–2.3</td>
<td>1.29 ± 0.73*</td>
<td>0.95 ± 0.23</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>95.1 ± 15.8</td>
<td>93.1 ± 12.0</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s·cm⁻²</td>
<td>1137 ± 387*</td>
<td>1567 ± 475</td>
</tr>
<tr>
<td>Arterial compliance, mmHg/ml</td>
<td>1.32 ± 0.39*</td>
<td>1.04 ± 0.10</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>75 ± 14*</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>6.8 ± 2.1*</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>Central circulation time, s, 14–28</td>
<td>12.1 ± 3.8*</td>
<td>19.4 ± 4.4</td>
</tr>
<tr>
<td>Central blood volume, ml/kg</td>
<td>18.4 ± 4.2*</td>
<td>23.4 ± 6.9</td>
</tr>
<tr>
<td>Plasma volume, ml/kg</td>
<td>50.9 ± 8.4*</td>
<td>44.5 ± 5.0</td>
</tr>
</tbody>
</table>

Data are given as means ± SD (median and total range for serum bilirubin). MELD, Model for End-Stage Liver Disease; n.a., not applicable. *P < 0.05 vs. controls.

**Study Protocol**

In the morning, all patients underwent hemodynamic investigations including determination of BRS and pulmonary investigations including DLCO and contrast-enhanced echocardiography (CEE).

**Hemodynamic investigations.** Hepatic veins, right atrium, and femoral artery were catheterized as described elsewhere (25). The hepatic venous pressure gradient (HVPG) was determined as the wedge minus free hepatic vein pressures. The hepatic blood flow, hepatic venous pressure gradient (HVPG) was determined as the femoral artery were catheterized as described elsewhere (25). The hepatic blood flow, hepatic venous pressure gradient (HVPG) was determined as the femoral artery were catheterized as described elsewhere (25). The hepatic blood flow, hepatic venous pressure gradient (HVPG) was determined as the femoral artery were catheterized as described elsewhere (25).

**Assays**

**Norepinephrine.** Plasma norepinephrine concentrations were determined by a commercial available ELISA kit (Labor Diagnostika Nord, Nordhorn, Germany). Intra-assay and interassay coefficients of variation were 10 and 15%, respectively, and the detection limit was 0.01 ng/ml.

**Renin.** The circulating plasma renin concentration was determined by a commercially available two-site immunoradiometric assay (IRMA; DGR International) as previously described (26). Samples were collected in ice-chilled test tubes containing aprotinin-heparin and EDTA. The detection limit was 0.31 pg/ml, intra- and interassay variations were 2%, and the median concentration in 536 healthy subjects was 26 pg/ml (range: 5.2–33.4 pg/ml).
intra-assay and interassay coefficients of variation were 4 and 10%, respectively.

**Aldosterone.** Plasma aldosterone was measured using a commercial kit (COAT-ACOUNT, Diagnostic Products, Los Angeles, CA). The detection limit was 11 pg/ml. Recovery was 87%. The intra-assay and interassay coefficients of variation were 3 and 5%, respectively.

**Endothelin-1.** We determined plasma endothelin concentrations by a commercial available ELISA kit (Biomedica Gruppe, Wien Austria). Intra-assay and interassay coefficients of variation were 4 and 6%, respectively, and the detection limit was 0.01 fmol/ml.

**Pro-ANP.** Plasma pro-atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations were determined by a commercial available ELISA kit (Biomedica Gruppe, Wien, Austria). Intra-assay and interassay coefficients of variation were 2 and 4%, respectively and the detection limit was 0.034 nmol/l.

**BNP.** BNP was measured by an automated two-site sandwich immunoassay technique using chemiluminescence (ADVIA Centaur, Siemens, Germany). The assay measures the physiologically active COOH-terminal peptide (77–108). The sensitivity of the assay was 2 pg/ml, and the intra- and interassay coefficients of variation were 1.2 and 2.3%, respectively (47).

**Oxygen inhalation.** After measurements of the baseline data, a sealed oxygen mask was placed over the nose and mouth of the supine patient and humidified 100% oxygen (15 l/min) was given for 20 min. At the end of that period, blood pressures, BRS, QT interval, and vasoactive substances were again measured.

**Statistical Analyses**

Data are presented as means ± SD or medians and interquartile ranges in case of a nonnormal distribution. Statistical analyses were performed by unpaired Student’s t-test or the Mann-Whitney test, ANOVA or ANOVA on ranks, paired Student’s t-test, or Wilcoxon’s test, as appropriate. Correlation analyses between independent variables were performed by the Spearman’s rank correlation test. A P value less than 5% was considered significant.

**RESULTS**

Patients with cirrhosis had significant portal hypertension, with a mean hepatic venous pressure gradient of 15.3 ± 6.3 mmHg, augmented hepatic perfusion and impaired liver function, as evaluated by the Child and MELD scores (Table 1). The patients also showed signs of vasodilatation with a reduced SVR and increased arterial compliance and a hyperdynamic circulation with increased CO and HR (Table 1).

**Lung Function**

Four patients had a positive CEE, indicative of presence of HPS. Spirometric data showed normal results except for five patients who were able to have a chronic obstructive lung disease with mild spirometric reduction. DLCO and DlCO/Va were significantly reduced in 31 and 37 of the patients, respectively (Table 2). PaO2 was below the lower normal reference threshold of 10.6 kPa in 13 patients and (A-a)Po2 was increased above 2.6 kPa in 27 patients (Table 3).

**Baroreflex Sensitivity**

The baseline BRS was significantly reduced in the cirrhotic patients compared with the controls (4.7 ± 0.8 vs. 10.3 ± 2.0 ms/mmHg, P < 0.001). Fig. 1. There was no significant difference in BRS according to presence of HPS as evaluated by CEE, the Child-Turcotte or MELD scores, or the presence of ascites. There were no significant correlations between baseline BRS and PaO2, (A-a)Po2, DLCO, or DlCO/Va. After 100% oxygen inhalation, BRS remained unchanged in the cirrhotic patients and was still significantly lower in the cirrhotic patients than in the controls (P < 0.005). After oxygen inhalation, arterial blood pressures increased slightly by 2–6% in both patients and controls, and HR decreased in both patients and controls, but the change was less pronounced in the patients, –3% vs. –10% in the controls (P = 0.02).

At baseline, BRS correlated with serum potassium (r = −0.41, P < 0.005), serum bilirubin (r = 0.30, P < 0.05), HR (r = −0.58, P < 0.0001), and AC (r = 0.30, P < 0.05).

**QT Interval**

The mean QTc and QTf intervals were significantly prolonged in the cirrhotic patients compared with the controls (P < 0.05, Table 4, Fig. 2). After oxygen inhalation, there was an insignificant trend toward a further prolongation of the QTc and QTf intervals (Table 4) in cirrhotic patients but not in controls. According to the median change in the QTc interval of 4.2 ms, the patients were divided into two groups. In the low-QTc interval group, median baseline QTc interval was significantly longer than in the high-QTc change interval (0.46 vs. 0.44 s, P < 0.005). The change in BRS was borderline significantly smaller in the low- than in the high-change QTc group (−0.2 vs. 2.0 ms/mmHg, P = 0.08). Baseline BRS correlated significantly with QT (r = 0.61, P < 0.0001) and QTf (r = 0.37, P < 0.01) intervals.

**Vasoactive Substances**

The plasma renin concentrations were significantly increased in patients with cirrhosis compared with controls (P < 0.005, Table 5). After oxygen inhalation, a small but significant decrease in renin concentration of 10% was seen in the cirrhotic patients (P < 0.001). Plasma renin concentrations fell significantly more in the cirrhotic patients than in the controls (P < 0.02, Table 5). At baseline plasma renin concentrations correlated with HVPg (r = 0.43, P < 0.002), systolic blood pressure (−0.66, P < 0.0001), plasma angiotensin II concentrations (r = 0.79, P < 0.0001), and plasma aldosterone concentrations (r = 0.78, P < 0.0001). There was no significant difference between plasma angiotensin II concentrations between patients and controls either at baseline or after oxygen inhalation. At baseline plasma angiotensin II concentrations correlated with serum sodium (r = −0.40, P < 0.005), Child and MELD scores (r = 0.30, P < 0.001), and the detection limit was 0.01 fmol/ml.

![Table 2. Spirometry, total lung capacity, and lung diffusing capacity of 43 patients](http://ajpgi.physiology.org/ Downloaded from http://ajpgi.physiology.org/ on April 29, 2017)
The plasma aldosterone concentrations were significantly increased in patients with cirrhosis compared with controls (P < 0.05, Table 5). A slight but significant fall was seen in the aldosterone concentrations in both cirrhotic patients and controls after oxygen inhalation (P < 0.01), but there was no significant difference in the reduction between the groups (Table 5). At baseline plasma aldosterone concentrations correlated with Child score (r = 0.41, P < 0.005), HVPG (r = 0.30, P < 0.03), RAP (r = 0.32, 0.02), systolic blood pressure (−0.57, P < 0.0001), CBV (ml/kg ideal body weight, r = −0.28, P < 0.05), QTc (r = 0.34, P < 0.02), and plasma aldosterone concentrations (r = 0.68, P < 0.0001).

The plasma aldosterone concentrations were significantly increased in patients with cirrhosis compared with controls (P < 0.05, Table 5). A slight but significant fall was seen in the aldosterone concentrations in both cirrhotic patients and controls after oxygen inhalation (P < 0.01), but there was no significant difference in the reduction between the groups (Table 5). At baseline plasma aldosterone concentrations correlated with Child score (r = 0.41, P < 0.005), HVPG (r = 0.30, P < 0.03), RAP (r = 0.32, 0.02), systolic blood pressure (−0.57, P < 0.0001), CBV (ml/kg ideal body weight, r = −0.28, P < 0.05), QTc (r = 0.34, P < 0.02), and plasma aldosterone concentrations (r = 0.68, P < 0.0001).

The plasma pro-ANP concentrations were significantly increased in patients with cirrhosis compared with controls (P < 0.01, Table 5). A slight but significant increase was seen in the pro-ANP concentrations in the cirrhotic patients after oxygen inhalation (P < 0.05). At baseline, plasma pro-ANP concentrations correlated with serum creatinine (r = 0.36, P < 0.02), serum sodium (r = −0.33, P < 0.03), serum albumin (r = −0.50, P < 0.001), HVPG (r = 0.30, P < 0.05), and ICG (r = −0.37, P < 0.02). There were no significant correlations of pro-ANP to BRS or RAP.

Plasma BNP concentrations were significantly higher in the cirrhotic patients than in the controls at baseline (P < 0.01) as well as during oxygen inhalation (P < 0.005). During oxygen inhalation BNP increased further in the cirrhotic patients (P < 0.001), whereas it remained unchanged in the controls. The patients were divided into two groups according to the median change in BNP of 6.7 pg/ml. In the low-BNP change group, the median change in BRS was borderline significantly lower than in the high-BNP change group (2.3 vs. 4.6 ms/mmHg, P = 0.07). At baseline, BNP concentrations correlated to indicators of liver dysfunction such as the MELD score (r = 0.45, P < 0.005) and serum albumin (r = −0.62, P < 0.0001), splanchnic hemodynamics such as ICG (r = −0.52, P < 0.0001) and HVPG (r = 0.43, P < 0.005), and cardiac and circulatory function such as HR (r = −0.40, P < 0.01), RAP (r = 0.33, P < 0.05), and QT interval (r = 0.35, P < 0.05). There were no significant correlations between BNP and pulmonary function. The change in BNP correlated significantly with baseline BRS (r = 0.33, P < 0.05).

Data are given as means ± SD. CEE, contrast-enhanced echocardiography.

*p < 0.05 vs. controls.

### Table 3. Blood gases, oxygen saturation, and alveolar-arterial oxygen gradient in 43 patients with cirrhosis and in 12 controls

<table>
<thead>
<tr>
<th></th>
<th>Patients with Cirrhosis (n = 43)</th>
<th>Controls (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial O₂ tension, kPa</td>
<td>11.5 ± 1.8</td>
<td>11.0 ± 1.2</td>
</tr>
<tr>
<td>Arterial O₂ saturation, %</td>
<td>96 ± 2</td>
<td>95 ± 4</td>
</tr>
<tr>
<td>Alveolar-arterial O₂ gradient, kPa</td>
<td>3.1 ± 1.8</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>Arterial CO₂ tension, kPa</td>
<td>4.5 ± 0.6*</td>
<td>5.5 ± 0.4</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.44 ± 0.05*</td>
<td>7.41 ± 0.01</td>
</tr>
<tr>
<td>Positive CEE, yes/no</td>
<td>4/39</td>
<td>0/12</td>
</tr>
</tbody>
</table>

### Table 4. Q-T interval, QTc, and QTf in 43 patients with cirrhosis and 12 controls at baseline and after oxygen inhalation

<table>
<thead>
<tr>
<th></th>
<th>Patients with Cirrhosis (n = 43)</th>
<th>Controls (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-T interval, s</td>
<td>0.409 ± 0.039</td>
<td>0.401 ± 0.030</td>
</tr>
<tr>
<td>Q-T interval, s-O₂</td>
<td>0.425 ± 0.044*</td>
<td>0.410 ± 0.025</td>
</tr>
<tr>
<td>QTc, s^{1/2}-O₂</td>
<td>0.453 ± 0.031*</td>
<td>0.409 ± 0.027</td>
</tr>
<tr>
<td>QTf, s^{2/3}-O₂</td>
<td>0.466 ± 0.056*</td>
<td>0.405 ± 0.011</td>
</tr>
<tr>
<td>QTf, s^{2/3}-O₂</td>
<td>0.439 ± 0.027*</td>
<td>0.406 ± 0.024</td>
</tr>
<tr>
<td>QTf, s^{2/3}-O₂</td>
<td>0.451 ± 0.049*</td>
<td>0.406 ± 0.008</td>
</tr>
</tbody>
</table>

Data are given as means ± SD. -O₂, after oxygen inhalation; QTc and QTf, heart rate-corrected QT interval. *P < 0.05 vs. controls; †P < 0.05 vs. baseline.

Fig. 1. Baroreflex sensitivity (BRS) in 43 patients with cirrhosis and controls at baseline and after 100% oxygen inhalation. *P < 0.001 vs. controls.

Fig. 2. Corrected QT (QTc) interval in 43 patients with cirrhosis and controls at baseline and after 100% oxygen inhalation. *P < 0.001 vs. controls.
There was no significant difference between circulating norepinephrine level between patients and controls. In the cirrhotic patients, plasma norepinephrine correlated with splanchnic hemodynamics such as hepatic blood flow \( (r = -0.38, P < 0.02) \) and mean arterial blood pressure \( (r = -0.39, P < 0.01) \) but not with BRS. There was no significant change in norepinephrine after oxygen inhalation.

There was no significant difference in ET-1 between patients and controls and no significant change in neither of the groups after oxygen inhalation. ET-1 correlated to indicators of metabolic liver function such as ICG clearance \( (r = -0.37, P < 0.02) \) and portal hypertension (postsinusoidal resistance, \( r = 0.36, P < 0.03 \)) but not to BRS. However, in patients with HPS, circulating ET-1 was significantly higher than in those without \( (6.9 \pm 1.3 \text{ vs. } 2.9 \pm 1.2 \text{ fmol/ml, } P < 0.0001) \).

### DISCUSSION

The main findings of the present study are the following: 1) BRS is significantly reduced in patients with cirrhosis and that pulmonary dysfunction is prevalent with 10% of the patients suffering from a HPS. However, we were unable to reveal a causal relationship between pulmonary dysfunction and the impaired BRS. 2) BRS was on the other hand associated with metabolic and hemodynamic characteristics of the liver disease. 3) After 100% oxygen inhalation, BRS remained low in the cirrhotic patients. 4) The QT interval was prolonged in the cirrhotic patients, and correlated with BRS, but oxygen inhalation had no effect on the adjusted QT interval. 5) Plasma concentrations of renin, aldosterone, pro-ANP, and BNP were increased in cirrhosis. After oxygen inhalation, renin and aldosterone concentrations decreased, whereas pro-ANP concentrations increased. No significant relations to the reduced BRS and vasoactive substances were seen.

It is well documented that patients with cirrhosis exhibit severe cardiovascular disturbances with impaired regulation of the systemic blood pressure, CO, and HR \( (17, 22, 36) \). This was confirmed by an increase both in BNP and pro-ANP and a relation to the change in BNP and BRS in our study. The entity cirrhotic cardiomyopathy reflects the notion that a latent cardiac dysfunction plays a role for the development of complications of cirrhosis and portal hypertension and the outcome in these patients \( (27, 48) \). Several studies have revealed an impaired cardiopulmonary baroreflex function with abnormal response to pharmacological vasodilatation and changes in posture \( (19, 23, 35) \). BRS is increasingly used as an indicator of the status of the cardiac autonomic control. Reduced BRS sensitivity has previously been described in these patients with relations to severity of the liver disease \( (3, 32, 37, 46) \). In cirrhotic patients, a low BRS indirectly expresses a reduced vagal tone and significantly contributes to the impaired cardiovascular regulation \( (2, 3, 10) \). In addition, cirrhotic patients have a pulmonary dysfunction with arterial hypoxemia and reduced lung diffusing capacity, since this is seen in more than 80% of the patients \( (31, 33, 49) \). The present article was based on the hypothesis that the reduced BRS could at least partly be attributed to arterial hypoxemia owing to the pulmonary dysfunction and that normalization of the low PaO_2 values would improve the BRS. This hypothesis lend substrate from the observation that arterial hypoxemia from a sojourn in high altitude or exposure to simulated altitudes (low oxygen pressure) reduces BRS in otherwise healthy individuals by ~30\% \( (43, 44) \). Results of several studies indicate that the changes in BRS are less pronounced after acute exposure of hypoxia and that BRS normalizes after returning to levels with normal oxygen pressure \( (12, 40) \). The mechanisms behind the reduction in BRS could be changes in cardiac sympathetic activation and parasympathetic withdrawal \( (43, 44) \). In our patients, hypoxia had no effect on circulating norepinephrine concentrations. However, baseline norepinephrine concentrations were not significantly increased in the patients, which could be explained by the relatively low number of Child class C patients. It has also been observed that patients with chronic obstructive pulmonary disease exhibit low BRS inversely related to pulmonary artery pressure \( (38) \). In these patients, the reduced BRS may be caused by a combination of pulmonary hypertension, hypoxia, and hypercapnia. In our cirrhotic patients, we were unable to increase the low BRS by inducing hypoxia with 100% oxygen inhalation. The impaired BRS in cirrhosis therefore appears refractory to changes in oxygenation and it is unlikely, therefore, that it is caused by a pulmonary dysfunction including arterial hypoxemia. The absence of direct correlations between oxygen saturation, lung \( DLCO/VA \), and \( (A-a)Po_2 \) and BRS supports this notion. However, since we found that a slight but insignificant trend toward an increase in BRS occurred in the patients after oxygen inhalation and that only one-third of the patients had significant hypoxia, it cannot be ruled out that oxygen inhalation in a population of patients with more severe pulmonary dysfunction and a higher frequency of HPS or prolongation of the oxygen supply would have had a more pronounced effect.

Reduced BRS seems an ominous sign in cirrhosis. Thus Genovesi et al. \( (10) \) recently showed that the reduced BRS in cirrhosis was significantly related to the degree of portal hypertension and survival. In our study we were unable to demonstrate a direct relation between the hepatic venous pressure gradient and BRS. On the other hand we found that the...
low BRS in the cirrhotic patients correlated with HR and AC, and after oxygen inhalation MAP increased significantly in the patients and the HR decreased. This indicates that, although the hemodynamic response was modest, it was possible to affect other components of the cardiovascular system by increasing the oxygen supply. Effects of oxygen supply have previously been reported but the results are inconsistent, some showing beneficial effects while others do not (18, 24). Taken together, it appears that all the cardiovascular effects of oxygen inhalation in cirrhosis are modest and temporary and that it may not be possible significantly to revert the hyperdynamic syndrome by this method.

A prolonged QT interval has been reported in several studies with relations to splanchnic and systemic hemodynamics and survival (13, 50, 51). In this study, we confirmed that prolongation of the QT intervals in patients with advanced cirrhosis correlates with BRS, indicators of liver dysfunction such as the MELD score, and central systemic hemodynamics such as CBV and SV. The QT interval also correlated with HR at baseline. After oxygen inhalation, the QTc and QTf intervals did not change significantly but the uncorrected QT interval increased further, possibly owing to the concomitant decrease in HR and increase in R-R interval. Results of previous studies have shown that in cirrhosis it is possible partly to normalize the prolonged QT interval by acute or chronic administration of beta-blockers (14, 52). However, the prolonged QT interval in cirrhosis seem refractory for treatment by oxygen supply. However, the significant associations between the prolonged QT interval on the one hand and the reduced BRS, low CBV, SV, and indicators of liver dysfunction on the other underline that the electromechanical disturbances are an integrated part of the hepatic and cardiovascular dysfunction in cirrhosis.

The hyperdynamic syndrome with the characteristic hemodynamic changes in cirrhosis is largely pertaining to a preferential arterial vasodilatation with a reduced SVR (17). Several vasoconstrictive counterregulatory systems are activated such as the RAAS, SNS, ANPs, and the endothelin system (28). The results of this study confirm the activation of several of these systems. In particular, the RAAS system was suppressible by oxygen inhalation whereas pro-ANP and BNP increased further. Significant correlations between the vasoactive substances and splanchnic and systemic hemodynamics indicate an intimate relation between these systems and the abnormal hemodynamic regulation. However, in this study we found no significant relations between the low BRS and the measured vasoactive substances. In experimental models of HPS, the endothelin system has been implicated in the pathophysiology (7). Overexpression of the vascular endothelial ET1 receptor in the lungs in animals with experimental HPS may lead to increased NO release after ET-1 stimulation and pulmonary vasodilatation (20). Our findings of increased circulating ET-1 concentrations in patients with HPS support this assumption. However, these pathophysiological mechanisms still need to be verified in human HPS.

In conclusion, the BRS is reduced in cirrhosis, but it is unrelated to the degree of pulmonary dysfunction. Oxygen inhalation failed to normalize the reduced BRS and the prolonged QT interval, indicating that pulmonary dysfunction and arterial hypoxemia per se plays a minor role in the abnormal cardiovascular regulation in cirrhosis and portal hypertension.

GRANTS
The study was supported by grants from The Hvidovre Hospital Research Foundation.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES