Cardiac sympathetic imaging with mIBG in cirrhosis and portal hypertension: relation to autonomic and cardiac function

Soren Møller,1 Christian Mortensen,1,2 Flemming Bendtsen,2 Lars T. Jensen,3 Jens P. Gøtze,4 and Jan L. Madsen1

1Centre of Functional Imaging and Research, Department of Clinical Physiology and Nuclear Medicine, 2Gastro Unit, Medical Division, Hvidovre Hospital, 3Department of Clinical Physiology and Nuclear Medicine, Glostrup Hospital, 4Department of Clinical Biochemistry, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

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Møller S, Mortensen C, Bendtsen F, Jensen LT, Gøtze JP, Madsen JL. Cardiac sympathetic imaging with mIBG in cirrhosis and portal hypertension: relation to autonomic and cardiac function. Am J Physiol Gastrointest Liver Physiol 303: G1228–G1235, 2012. First published September 27, 2012; doi:10.1152/ajpgi.00303.2012.—Autonomic and cardiac dysfunction is frequent in cirrhosis and includes increased sympathetic nervous activity, impaired heart rate variability (HRV), and baroreflex sensitivity (BRS). Quantified 123I-metaiodobenzylguanidine (mIBG) scintigraphy reflects cardiac noradrenaline uptake, and in patients with cardiac failure it predicts outcome. In this study, we aimed to investigate cardiac sympathetic neuronal function in cirrhosis by mIBG scintigraphy in relation to cardiovascular function. Ten patients with alcoholic cirrhosis and 10 age- and sex-matched healthy controls participated in the study. Heart/mediastinum (H/M) ratios of mIBG uptake were calculated 15 and 230 min after intravenous injection of mIBG. Furthermore, washout rate (WOR) of mIBG was calculated. The patients underwent a liver vein catheterization with determination of splanchic and systemic hemodynamics and measurement of HRV and BRS. mIBG-scintigraphy revealed significantly increased WOR in patients with cirrhosis compared with controls (P < 0.005), whereas H/M uptakes were equal in the groups. Forty percent of the patients had reduced uptake of mIBG in the infero-lateral segment of the left ventricle. WOR correlated significantly with central circulation time, an estimate of central hypovolemia (r = −0.64, P < 0.05) and frequency-corrected QT interval (r = 0.71, P = 0.01). Patients with cirrhosis had significantly decreased HRV and BRS correlating with indicators of abnormal catecholamine uptake by mIBG although the catecholamine level was normal in the patients. In conclusion, in alcoholic cirrhosis, mIBG scintigraphy reveals autonomic dysfunction and impaired myocardial distribution of sympathetic nervous activity. It is associated to indicators of central hypovolemia, QT interval, and decreased HRV and BRS. Measurement of myocardial catecholamine uptake by mIBG may add important information on autonomic and cardiac dysfunction in cirrhosis.

Address for reprint requests and other correspondence: S. Møller, Ctr. of Functional Imaging and Research, Dept. of Clinical Physiology and Nuclear Medicine, Hvidovre Hospital, Kettegaard Alle 30, DK-2650 Hvidovre, Copenhagen, Denmark (e-mail: soeren.moller@hvh.regionh.dk).

Sympathetic nervous system (SNS) (10, 33, 41). The recently described, cirrhotic cardiomyopathy is seen in more than 50% of the patients and includes diastolic and systolic dysfunction as well as prolonged QT-interval (29, 43). Cirrhotic cardiomyopathy may contribute to development of complications such as renal failure and reduced survival (35). SNS is often activated in decompensated patients reflected by increased circulating catecholamine levels and downregulation of β-receptors in various organs including the heart (14).

123I-metaiodobenzylguanidine (mIBG) is a physiological analog of noradrenaline. γ-Camera imaging with mIBG reflects noradrenaline concentrations, storage, release, and uptake and thereby the β-receptor density (5). Patients with chronic heart failure typically exhibit reduced presynaptic noradrenaline uptake and postsynaptic β-receptor density (5). Unlike noradrenaline, mIBG is not metabolized, allowing it to be imaged, and myocardial uptake and distribution can therefore be visually assessed. mIBG uptake is semiquantified by calculating a heart-to- mediastinum ratio, which provides a highly reproducible index of cardiac sympathetic activity. By comparing early and delayed activities, the mIBG washout rate (WOR) from the myocardium can be derived. The WOR reflects retention of noradrenaline by sympathetic neurons (8). Single-photon emission computerized tomography (SPECT) images furthermore allow evaluation of the distribution of regional cardiac sympathetic activity. In patients with cardiac failure, impaired adrenergic innervation as assessed by mIBG imaging is strongly related to survival (5, 18).

In the present study, we aimed to investigate cardiac noradrenaline uptake by mIBG scintigraphy in patients with cirrhosis and to assess its relation to liver dysfunction and other neurohumoral variables of autonomic dysfunction, including baroreflex regulation and HRV.

MATERIALS AND METHODS

Study population. Ten consecutive patients from the outpatient clinic were referred to a liver vein catheterization and consecutively enrolled in the study. All patients had suspicion of portal hypertension and had verified alcoholic cirrhosis, i.e., an alcohol consumption exceeding 50 g of 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 accepted clinical and biochemical criteria and presence of portal hypertension. Patients were stratified according to the modified Child-Turcotte score. Five patients had ascites confirmed by ultrasonography. Diuretics were stopped 24 h before the study. None of the patients were taking cardiovascular medication, β-blockers, or calcium channel blockers. None of the patients had signs of infections or received antibiotics within the previous 3 wk before the study or
during the study period. An age-matched control group consisted of 10 healthy volunteers without liver disease. Controls were recruited from age- and sex-matched healthy staff at Hvidovre Hospital. None were 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. H-3–2009-133). No complications or side effects were encountered during the study.

Study protocol. All patients underwent a hemodynamic investigation in the morning after an overnight fast and at least 1 h resting in the supine position. Hepatic veins, right atrium (RA), and femoral artery were catheterized as described elsewhere (27). The hepatic venous pressure gradient was determined as the wedged minus free hepatic vein pressures. The hepatic blood flow, postinsufflation resistance, indocyanine green clearance, and galactose elimination capacity were determined as previously described (27, 31).

Cardiac output (CO) was measured by the indicator dilution method, as previously described (27). Systemic vascular resistance (SVR) expressed in dynes·s·cm⁻² was assessed as 80 × (mean arterial pressure-right atrial pressure/CO); pressures were expressed in mmHg and CO in liters per minute. The central circulation min time (CCT) representing the mean indicator sojourn in the central blood volume (CBV) were both assessed in accordance with the kinetic theory, as described earlier (27, 30). Reduced CCT and CBV are both indicative of central hypovolemia. An indwelling polyethylene catheter was placed in the femoral artery, and the arterial blood pressures determined by ECG monitoring. Partial pressure of arterial oxygen (PaO₂), been measured by ABL-510 (Radiometer, Copenhagen, Denmark). The arterial-arteriole oxygen gradient (AaPO₂) was calculated from the alveolar gas equation: AaPO₂ = [FiO₂ (PB-47) - (PaCO₂/R - FiO₂, (1 - R) (PaCO₂/R)] - PaO₂ (31). mIBG scintigraphy. The day after the hemodynamic investigation, patients and controls underwent a mIBG myocardial scintigraphy. Briefly, after an overnight fast, 150–200 MBq of ¹²³I-metaiodobenzyl-guanidine (AdreView; GE Healthcare, Little Chalfont, UK) were injected intravenously. Fifteen and 230 min after injection, planar and tomographical (SPECT) scintigraphy were performed by a two-headed γ-camera (Infiniti; General Electric Medical Systems, Milwauk-kee, WI), using low-energy, high-resolution collimators. In planar recordings, a matrix of 256 by 256 and acquisition time of 10 min was used. The heart/mediastinum ratio (H/M) was determined from the counts/pixel in a visually drawn heart region of interest divided by the counts/pixel in a mediastinal 7 × 7 pixels region of interest. WOR corrected for background was calculated as number of counts in the anterior projection at 15 min minus the counts at 230 min, the background (mediastinal) count subtracted from each count: WORh = [(H/M of initial image – H/M of delayed image)/(H/M of initial image)] × 100% (8). The count rate at 230 min was corrected for radioactive decay.

Noninvasive measurements. In relation to the mIBG scintigraphy, the patients and controls underwent a noninvasive investigation of hemodynamics (blood pressure, CO, SVR, HRV, and BRS). All individuals were monitored after 1 h at rest for 30 min in the supine position and after 20 min of 60° tilting. A commercially available monitoring system [Task Force Monitor (TFM); CNSystems, Graz, Austria] was used. This system integrates ECG, oscillometric, continuous plethysmographic blood pressure registration, and impedance cardiography, allowing analysis of the power spectral analysis of HRV and BRS (9). The TFM automatically provides the 0.05–0.17-Hz [low-frequency (LF) band] and 0.17–0.40-Hz band [high-frequency (HF) band] of HR interval variability in normalized units (LFnu-RRI and HFnu-RRI, respectively, where RR is R-wave to R-wave) and the 0.05-0.17-Hz band of systolic (SBP) and diastolic blood pressure (DBP) variability in absolute values (LFsbBP and LFdbBP, respectively) and normalized units (LFnu-sSBP and LFnu-

**DBP**, respectively, using power spectral analysis, applying an autoregressive methodology (1, 9). Normalized and absolute values were applied. Additionally, BRS was automatically assessed by the TFM using the sequence method (40). For head-up tilt, we used a motorized table with footboard support and security straps at the hip.

**QT interval.** We recorded ECG by conventional noncomputerized equipment (Megacart; Siemens-Elema, Erlangen, Germany). The QT interval was determined on the ECG (50 mm/s) as described elsewhere (13). QT intervals were frequency-corrected (QTc) with the Bazett formula: QTc = Q-T(RR)⁻¹/², where RR is the R-R interval in seconds. Prolonged QTc was defined as QTc > 0.440 s⁻¹/² (13). The QT interval was determined blindly, i.e., with no knowledge of the diagnosis or clinical and hemodynamic variables.

Assays. Renin concentrations were determined using a commercially available two-site immunonadiometric assay (DGR International, Marburg, Germany). Samples were collected in ice-chilled test tubes containing aprotinin-heparin and EDTA. The detection limit was 0.31 pg/ml, and intra- and interassay variabilities were less than 2% (28). The reference interval (mean ± range) was 26 (5.2–33.4) pg/ml.

Plasma adrenaline and noradrenaline were analyzed by radio immunoassay using a commercially available kit (2-Cat RIA, BA-1500; Labor Diagnostika Nord, Nordhorn, Germany), calibrated by their own validated standards. The tubes used to measure plasma adrenaline and noradrenaline were prechilled, containing 100 µl glutathione and EGTA, centrifuged at 4°C and stored at −80°C. The samples were stored for up to 1 yr, which may reduce the content of intact immunoreactive adrenaline and noradrenaline. However, the decrease in immunoactivity was so low, as judged on the normal controls, that it did not influence the results.

Pro-α1 natriuretic peptide (proANP) was measured by an automated method that detects the midregion of the prohormone (BRAHMS). The method has been validated previously (16, 25). Pro-B-type natriuretic peptide was measured on a Modular E platform (Roche, Jena, Switzerland); this assay has been used for more than a decade as the “gold standard” in biochemical assessment of heart failure patients.

**Statistics.** Data are presented as means ± SD or medians and interquartile ranges as appropriate. Statistical analyses were performed by unpaired Student’s t-test or the Mann-Whitney test, the ANOVA, or ANOVA on the ranks, 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. The χ²-test was used to compare proportions between groups. A P value <0.05 was considered significant.

**RESULTS**

Clinical, anthropometric, biochemical, and hemodynamic characteristics of the 10 patients with cirrhosis are shown in Table 1. All patients had significant portal hypertension with a hepatic venous pressure gradient between 6 and 22 mmHg.

The mIBG scintigraphy revealed significantly increased WOR in patients with cirrhosis, 19.5% compared with controls, 10.5% (P < 0.005) (Table 2 and Fig. 1). Early and late H/M ratios did not significantly differ between patients and controls. In the cirrhotic patients, uncorrected WOR correlated significantly with CCT (r = −0.64, P < 0.05) and QT intervals: QT (r = 0.64, P < 0.04), QTc (r = 0.70, P < 0.02), and QTf (r = 0.71, P < 0.01, Fig. 2). Moreover, H/M 15 was correlated significantly with pH (r = 0.72, P < 0.01) and H/M 230 with pCO₂ (r = 0.72, P < 0.01) and AaPO₂ (r = 0.78, P < 0.005). Stratification with respect to the absence or presence of ascites did not reveal significant differences with respect to H/M or WOR. SPECT images showed that 40% of the patients had reduced uptake of mIBG in the inferolateral segment of the...
Table 1. Clinical, anthropometric, and biochemical characteristics of 10 patients with cirrhosis and 10 healthy controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 10)</th>
<th>Controls (n = 10)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Height, cm</td>
<td>171 ± 7</td>
<td>172 ± 14</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.2 ± 15.3</td>
<td>77.3 ± 18.2</td>
<td></td>
</tr>
<tr>
<td>Sex, m/f</td>
<td>5/5</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>55.6 ± 10.0</td>
<td>48.1 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4 ± 4.4</td>
<td>25.7 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Ascites, no/yes</td>
<td>5/5</td>
<td>10/0</td>
<td></td>
</tr>
</tbody>
</table>

Blood biochemistry

- Blood hemoglobin, mmol/l (7.0–10.9)*: 7.6 ± 0.8
- Plasma coagulation factors II, VII, and X, units (0.70–1.30): 0.57 ± 0.14
- Serum albumin, μmol/l (540–800): 527 ± 140
- Serum sodium, mmol/l (136–146): 138 ± 2
- Serum ALAT, U/l (10–50): 34 ± 19
- Galactose elimination capacity, mmol/min, >1.7 (men); >1.4 (women): 1.93 ± 0.53
- Child score: 7.1 ± 2.1

Hemodynamics

- Hepatic venous pressure gradient, mmHg: <5
- Postsinusoidal resistance, mmHg·min⁻¹·l⁻¹: 12.3 ± 5.5
- Right atrium pressure, mmHg: <5
- Hepatic blood flow, l/min (0.5–2.3): 1.24 ± 0.38
- Indocyanine green clearance, ml/min (300–700): 246 ± 127
- Cardiac output, l/min: 5.5 ± 0.9
- Central circulation time, s (14–28): 16.0 ± 2.6
- Plasma volume, l: 3.74 ± 0.74
- Systemic vascular resistance, dyn·s·cm⁻³: 1337 ± 422
- Central blood volume, l: 1.47 ± 0.28

QT-intervals

- QT, ms: 0.40 ± 0.03
- QTc, ms¹/₂: 0.45 ± 0.02
- QTc, ms¹/₃: 0.44 ± 0.02

Arterial gas tensions

- Arterial pH: 7.43 ± 0.04
- Arterial O₂ tension, kPa: 10.7 ± 1.5
- Arterial O₂ saturation, %: 95 ± 2
- Alveolar-arterial O₂ gradient, kPa: 3.4 ± 1.5
- Arterial CO₂ tension, kPa: 4.7 ± 0.3
- Arterial standard HCO³⁻, meq/l: 24.1 ± 2.7

Values are means ± SD. Reference interval in parentheses. BMI, body mass index; ALAT, alanine aminotransferase.

left ventricle, whereas all healthy controls presented normal SPECT studies without defects (P = 0.02, Fig. 3). We observed no significant differences with respect to metabolic liver function, portal pressure, systemic hemodynamics, or natriuretic peptides in patients with reduced uptake compared with those with normal uptake.

Table 2. Early (15 min) and late (230 min) heart/mediastinum ratios of mIBG uptake and washout rates of mIBG in 10 patients with cirrhosis and 10 healthy controls

<table>
<thead>
<tr>
<th>Ratio/Rate</th>
<th>Patients with Cirrhosis (n = 10)</th>
<th>Controls (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart/mediastinum ratio</td>
<td>1.90 (1.8–2.0)</td>
<td>1.75 (1.7–2.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart/mediastinum ratio</td>
<td>2.05 (1.8–2.1)</td>
<td>1.90 (1.7–2.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Washout rate (without BC)</td>
<td>19.5 (12.0–24.0)</td>
<td>10.5 (6.0–11.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Washout rate (with BC)</td>
<td>21.0 (3.0–28.0)</td>
<td>0.0 (0.0–6.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Values are medians and interquartile ranges. mIBG, 123I-metaiodobenzylguanidine.
HF component in cirrhosis than in the controls \((P < 0.05 - P < 0.005)\) both presented as normalized and absolute values. LF/HF was significantly decreased in cirrhosis \((P < 0.05 - P < 0.005)\), whereas the VLF component showed no difference between patients and controls. BRS was significantly reduced in the cirrhotic patients \((P < 0.05)\) and after tilt; BRS decreased in the controls \((P < 0.01)\), whereas it remained unaltered in the cirrhotic patients. There were significant differences between patients and controls with respect to LF/HF of HRV \((P < 0.05)\), LF, HF, and LF/HF components of blood pressure variability \((P < 0.05 < 0.01)\) and BRS \((P < 0.05)\). In the patients, H/M 15 and H/M 230 correlated in particular with the HF component \(r = -0.75, P < 0.01\) and VLF component \(r = -0.79, P < 0.005\). H/M 15 correlated significantly with BRS after head-up tilt \(r = -0.67, P < 0.05\). At baseline, BRS correlated with pro-brain natriuretic peptide (BNP) \(r = 0.86, P < 0.005\).

Circulating hormones in patients and controls are presented in Table 5. There were no significant differences in the circulating catecholamines or renin between patients and controls. However, circulating noradrenaline correlated significantly with WOR \(r = 0.77, P = 0.01\). ProANP and proBNP were significantly increased in patients with cirrhosis \((P < 0.001)\) but did not correlate with WOR or H/M ratio. ProANP correlated with SVR \(r = 0.64, P < 0.05\) and proBNP with QTf \(r = 0.69, P < 0.05\). At baseline circulating adrenalin correlated with the LF as well as the HF component of arterial blood pressure \(r = -0.79\) and \(r = -0.75, P < 0.005\). Circulating noradrenaline and renin correlated with LF and HF components of HRV \(r = 0.71, P < 0.01\).

After head-up tilt, HR changed significantly in both patients and controls, whereas MAP only increased in the controls \((P < 0.001, Table 3)\). LF/HF increased in both patients and controls \((P < 0.05)\). LF-dBP and VLF-sBP decreased in the controls after tilt \((P < 0.05)\), whereas there was no significant difference in the patients (Table 4). In the controls, BRS decreased \((P < 0.05)\), whereas it was unaltered in the patients (Table 4).

**DISCUSSION**

In this study, we attempted to evaluate autonomic nervous function by mIBG scintigraphy in relation to other markers and measures of autonomic dysfunction in alcoholic cirrhosis. The main findings of our study were that, in cirrhosis 1) the WOR is increased and the myocardial distribution of sympathetic activity is abnormal; 2) WOR correlates with indicators of central hypovolemia, electrophysiological abnormalities, and hyperventilation; 3) a differential response to head-up tilt is present in cirrhosis; and 4) indicators of abnormal HRV and BRS also correlate with measures of impaired retention and cardiac mIBG uptake in cirrhosis.

mIBG scintigraphy has hitherto been used mainly in the management of patients with heart failure and as an important research tool (18). Recently, results of mIBG scintigraphy have shown to provide prognostic information, and a clear association has been documented between severity of myocardial neuronal dysfunction and risk of cardiac death (5, 8, 18). Patients with chronic left ventricular dysfunction are characterized by a significant reduction of presynaptic norepinephrine uptake and reduced postsynaptic β-adrenergic density together with general increased sympathetic activity in the heart.
and in the circulation (5). This corresponds with downregulation of myocardial β-adrenoceptor density, which is also seen both experimentally and in patients with cirrhosis (12, 22). Because downregulation of β-adrenoceptors is seen both in patients with hypertrophic cardiomyopathy and in cirrhosis, it should be considered a general nonspecific response to locally increased amount of noradrenaline in the synaptic cleft. The increased sympathetic nervous activity observed in chronic heart failure as well as in decompensated cirrhosis is the consequence of several mechanisms, including increased sympathetic outflow, altered neuronal noradrenaline reuptake, and facilitation of cardiovascular response to sympathetic stimulation by the renin-angiotensin-aldosterone system (5). It should be noted that mIBG scintigraphy in patients treated with β-blockers may give other results than in patients without medication. None of our patients were treated with β-blockers, but studies of mIBG scintigraphy in the search for responders to β-blocker treatment are warranted. The myocardial uptake and distribution is assessed by mIBG and can be visually displayed in a polar map allowing evaluation of regional sympathetic activity (Fig. 3). mIBG uptake is semiquantified by calculating the H/M ratio and WOR, which provide a highly reproducible index of cardiac sympathetic activity (8). To our knowledge, assessment of autonomic nervous function by mIBG myocardial scintigraphy in cirrhosis has only been attempted previously in one study (17). In that study, the authors did not find significant changes in early and late H/M ratio but significantly higher WOR in cirrhotic patients correlating with plasma levels of noradrenaline, albumin, coagulation factor 2, 7, and 10, and Child score. The authors conclude that autonomic abnormalities even in early cirrhosis can be detected by mIBG myocardial scintigraphy (17). In our study, we extended this approach to a group of cirrhotic patients and controls well characterized with respect to hemodynamics, pulmonary function, cardiac and autonomic function, and neurohumoral abnormalities. In our patients, the increased mIBG WOR correlated with CCT, which reflects the indicator sojourn through the central blood volume and thereby central hypovolemia (32). This relation lends further support to the assumption of an important link between autonomic dysfunction and development of central hypovolemia in cirrhosis. This also corresponds with our previous findings of CCT as an independent prognostic marker in cirrhosis (26). Although mIBG WOR and H/M ratio of mIBG uptake are strong predictors of mortality in cardiac heart failure, it still remains to be shown whether this is also the case in patients with cirrhosis. Cirrhotic cardiomyopathy denotes an entity with a combined systolic and diastolic dysfunction and prolonged QT interval (29). In patients with cirrhosis, the prolonged QT interval is associated with poorer survival (3). The relation of the QT interval and the WOR of mIBG as found in the present study most likely reflects that the abnormalities in presynaptic norepinephrine uptake and postsynaptic β-adrenoceptor density play important pathophysiological roles in the QT interval prolongation. Approximately 40% of our patients had abnormal distribution of sympathetic activity, which has not previously been described. It is conceivable that this abnormal sympathetic activity plays a role in the pathophysiology of the electrophysiological

Table 3. Hemodynamic characteristics as assessed by the TASK FORCE Monitor in 10 patients with cirrhosis and in 10 healthy controls

<table>
<thead>
<tr>
<th>Patients with Cirrhosis (n = 10)</th>
<th>Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>Tilt</td>
</tr>
<tr>
<td>RR-Interval, ms</td>
<td>852 ± 147†</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>73 ± 12‡</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85 ± 16</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>56 ± 23‡</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.1 ± 1.6</td>
</tr>
<tr>
<td>EDI, ml/m²</td>
<td>51 ± 19‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.005 vs. supine position; †P < 0.001 vs. supine position. ‡P < 0.01 vs. controls. MAP: mean arterial blood pressure; EDI: end-diastolic volume index.
Changes and cardiac dysfunction in cirrhosis. We found no significant relation of abnormal distribution of sympathetic activity to patient characteristics, but the size of the material is too limited to draw final conclusions on the pathophysiological and clinical impact of the scintigraphic defects.

Previous studies using MRI have shown functional and morphological myocardial changes in patients with advanced alcoholic liver disease (23, 38). However, even in patients with early disease of other etiologies such as primary biliary cirrhosis, cardiac function as well as autonomic function seem impaired (19). It is conceivable that other mechanisms than the development of cirrhosis and portal hypertension may play a role in other types of chronic liver disease in the initiation and perpetuation of the cardiovascular dysfunction (15).

A considerable number of patients with cirrhosis have pulmonary dysfunction with abnormal gas exchange and metabolic disturbances (4, 36), resulting in patients with advanced disease is hyperventilation with development of respiratory alkalosis (4). Our findings of relations between H/M ratio of mIBG uptake and changes in pH and lung diffusion impairment, as assessed by AaPO2 and late retention of mIBG, point to pulmonary dysfunction as at least a potential contributing factor or at least a factor developing simultaneously with autonomic dysfunction.

There are several reports in the literature on autonomic dysfunction and impaired cardiovascular control. Thus impaired blood pressure regulation, BRS, and HRV have been extensively described in cirrhosis (2, 11, 20, 24, 34). As it appears from Table 4, patients with cirrhosis exhibit significantly impaired autonomic function relating to sympathetic as well as vagal component and the sympatho-vagal imbalance of the autonomic nervous system. These results are in agreement with previous observations in similar patient populations (21, 24).

Several variables pertaining to a sympatho-vagal imbalance correlated significantly with H/M ratios of mIBG uptake as obtained by mIBG scintigraphy and suggest that decreased HRV is also reflected by the abnormal mIBG uptake in the heart in contrast to what has previously been reported (17). In analogy with the present findings, we and others have previously found altered response to head-up tilt in cirrhotic patients, suggesting impaired cardiovascular regulation and myocardial contractility (20, 37). In addition, we and others have previously reported decreased BRS in cirrhosis (34, 39, 42). This was confirmed in the present study. Whereas BRS decreases in the controls during head-up tilt, no change was seen in cirrhosis after this procedure, supporting impaired cardiovascular control. Thus impairment correlated significantly with H/M ratio of mIBG uptake 15, indicating that, in addition to the baroreceptor dysfunction, abnormal catecholamine kinetics in the heart may also contribute to the impaired cardiovascular regulation in cirrhosis.

All patients in the present study had alcoholic cirrhosis and portal hypertension, and it cannot be ruled out whether mIBG scintigraphy in patients with other etiologies to chronic liver disease would have gained other results partly because of differences in the degree and type of autonomic dysfunction. Nevertheless, studies of mIBG scintigraphy would be of inter-

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### Table 4. Variability of heart rate and blood pressure and BRS as assessed by the TASK FORCE Monitor in 10 patients with cirrhosis and in 10 healthy controls

<table>
<thead>
<tr>
<th>Patients with Cirrhosis (n = 10)</th>
<th>Controls (n = 10)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine</strong></td>
<td><strong>Tilt</strong></td>
<td><strong>Supine</strong></td>
</tr>
<tr>
<td><strong>VLF-RRI, ms</strong></td>
<td>156 (44–295)†</td>
<td>245 (64–1432)</td>
</tr>
<tr>
<td><strong>LF-RRI, ms</strong></td>
<td>130 (56–259)§</td>
<td>131 (37–258)§</td>
</tr>
<tr>
<td><strong>HF-RRI, ms</strong></td>
<td>70 (33–327)</td>
<td>28 (8–380)</td>
</tr>
<tr>
<td><strong>LHF-HF-RRI, ms</strong></td>
<td>1.35 (0.61–2.38)</td>
<td>1.54 (0.51–6.07)</td>
</tr>
<tr>
<td><strong>LF-dBP, mmHg</strong></td>
<td>0.9 (0.5–2.3)†</td>
<td>1.1 (0.5–1.3)*</td>
</tr>
<tr>
<td><strong>HF-dBP, mmHg</strong></td>
<td>1.0 (0.1–1.7)†</td>
<td>0.6 (0.4–0.8)*</td>
</tr>
<tr>
<td><strong>LF/HF-dBP</strong></td>
<td>1.18 (0.57–1.90)§</td>
<td>1.83 (1.02–2.71)*</td>
</tr>
<tr>
<td><strong>LF/HF</strong></td>
<td>0.60 (0.41–0.86)†</td>
<td>0.79 (0.56–1.98)*</td>
</tr>
<tr>
<td><strong>LF/HF-sBP</strong></td>
<td>3.1 (2.0–7.6)</td>
<td>2.5 (1.3–3.9)</td>
</tr>
<tr>
<td><strong>LF/HF-HF-sBP</strong></td>
<td>1.8 (0.9–4.3)*</td>
<td>1.4 (1.0–2.9)§</td>
</tr>
<tr>
<td><strong>HF-sBP, mmHg</strong></td>
<td>2.7 (2.0–5.2)†</td>
<td>1.1 (0.7–2.4)*</td>
</tr>
<tr>
<td><strong>LF/HF-sBP</strong></td>
<td>0.94 (0.43–1.31)*</td>
<td>1.55 (0.84–2.16)*</td>
</tr>
<tr>
<td><strong>LF/HF</strong></td>
<td>0.51 (0.39–0.94)*</td>
<td>0.74 (0.57–1.64)*</td>
</tr>
<tr>
<td><strong>BRS slope-up, ms/mmHg</strong></td>
<td>10.2 (7.6–13.5)†</td>
<td>7.2 (4.7–11.6)</td>
</tr>
<tr>
<td><strong>BRS slope down, ms/mmHg</strong></td>
<td>9.9 (7.3–20.1)</td>
<td>7.2 (4.6–11.6)</td>
</tr>
<tr>
<td><strong>BRS total, ms/mmHg</strong></td>
<td>10.8 (7.4–15.0)†</td>
<td>6.6 (4.7–10.7)</td>
</tr>
</tbody>
</table>

\( \text{Values are medians and interquartile ranges. } ^{*}P < 0.05 \text{ vs. supine position}; ^{†}P < 0.05 \text{ vs. controls}; ^{‡}P < 0.01 \text{ vs. controls}. ^{§}P < 0.05 \text{ vs. controls after tilt; }^{d}P < 0.01 \text{ vs. controls after tilt. }^{*} \text{Very-low frequency (VL}F) \text{ of variability of components of heart rate (RRI), diastolic blood pressure (}d\text{BP), and systolic blood pressure (}s\text{BP). }^{b} \text{Low frequency (LF) of RRI, }d\text{BP, and }s\text{BP. }^{c} \text{High frequency (HF) of RRI, }d\text{BP, and }s\text{BP. BRS, baroreflex sensitivity.} \)
establish in the risk assessment before invasive procedures such as liver transplantation or TIPS, where cardiac dysfunction has been shown to be of importance (6, 7).

In conclusion, results of mIBG scintigraphy in alcoholic cirrhosis revealed autonomic and cardiac dysfunction and abnormal cardiac distribution of sympathetic activity. This seems to be associated with central hypovolemia, QT interval prolongation, and decreased HRV and BRS. Measurement of myocardial catecholamine uptake may contain important additional information on electrophysiological changes, and this tool should be used in future research on autonomic and cardiac dysfunction in cirrhosis.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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