Cardiac sympathetic imaging with $m$IBG in cirrhosis and portal hypertension: 
Relation to autonomic and cardiac function

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autonomic dysfunction
Abstract

Autonomic and cardiac dysfunction is frequent in cirrhosis, and includes increased sympathetic nervous activity, impaired heart rate variability (HRV) and baroreflex sensitivity (BRS). Quantified $^{123}$I-metaiodobenzylguanidine ($m$IBG) 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 $m$IBG 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 $m$IBG uptake were calculated 15 and 230 minutes after intravenous injection of $m$IBG. Furthermore, washout rate (WOR) of $m$IBG was calculated. The patients underwent a liver vein catheterization with determination of splanchnic and systemic haemodynamics and measurement of HRV and BRS. $m$IBG-scintigraphy revealed significantly increased WOR in patients with cirrhosis compared to controls ($p<0.005$), whereas H/M-uptakes were equal in the groups. Forty percent of the patients had reduced uptake of $m$IBG in the infero-lateral segment of the left ventricle. WOR correlated significantly with central circulation time, an estimate of central hypovolaemia ($r=-0.64$, $P<0.05$) and frequency-corrected QT$_F$ interval ($r=0.71$, $p=0.01$). Patients with cirrhosis had significantly decreased HRV and BRS correlating with indicators of abnormal cathecholamine up-take by $m$IBG although the catecholamine level was normal in the patients.

In conclusion, in alcoholic cirrhosis, $m$IBG scintigraphy reveals autonomic dysfunction and impaired myocardial distribution of sympathetic nervous activity. It is associated to indicators of central hypovolaemia, QT interval, decreased HRV and BRS. Measurement of myocardial catecholamine-uptake by $m$IBG may add important information on autonomic and cardiac dysfunction in cirrhosis.
Abbreviations

BRS: Baroreflex sensitivity
CBV: Central blood volume
CCT: Central circulation time
CO: Cardiac output
dBP: Diastolic blood pressure
EDI: End-diastolic volume index
GEC: Galactose elimination capacity
HBF: Hepatic blood flow
HF: High frequency
H/M: Heart/mediastinum ratio
HR: Heart rate
HRV: Heart rate variability
ICG: Indocyanine green clearance
LF: Low frequency
MAP: Mean arterial blood pressure
mIBG: $^{123}$I-metaiodo-benzyl-guanidine
RA: Right atrium
PSR: Post-sinusoidal resistance
sBP: Systolic blood pressure
SNS: Sympathetic nervous system
SPECT: Single photon emission computerised tomography
SV: Stroke volume
SVR: Systemic vascular resistance
TFM: Task force monitor
VLF: Very low frequency
WOR: Washout rate

Key words

Liver failure, autonomic dysfunction, SPECT, cirrhotic cardiomyopathy, baroreflex sensitivity, sympathetic nervous system, heart rate variability.
Introduction

Autonomic and cardiac dysfunction is frequent in cirrhosis, and includes impaired baroreflex sensitivity (BRS) and heart rate variability (HRV) in the setting of increased activity of the 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 down-regulation of betareceptors in various organs including the heart (14).

$^{123}$I-metaiodobenzylguanidine (mIBG) is a physiologic analogue of noradrenaline. Gamma camera imaging with mIBG reflects noradrenaline concentrations, storage, release, and uptake and thereby the betareceptor density (5). Patients with chronic heart failure typically exhibit reduced pre-synaptic noradrenaline up-take and post-synaptic betareceptor density (5). Unlike noradrenaline, mIBG is not metabolized, allowing it to be imaged and myocardial uptake and distribution can therefore be visually assessed. mIBG up-take 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 wash-out 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 up-take 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 out-patients clinic were referred to a liver vein catherization 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 alcohol per day for more than five years. All patients had abstained from alcohol for at least two months 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 hours 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 the previous three weeks 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 haemodynamic investigation in the morning after an overnight fast and at least one hour resting in the supine position. Hepatic veins, right atrium (RA), and femoral artery were catheterised as described elsewhere (27). The hepatic venous pressure gradient was determined as the wedged minus free hepatic vein pressures. The hepatic blood flow (HBF), post-sinusoidal resistance (PSR) indocyanine green clearance (ICG), and galactose elimination capacity (GEC) 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⁻⁵ was assessed as 80 x (mean arterial pressure-right atrial pressure/CO), pressures were expressed in mmHg, and CO in litres per minute.

The central circulation 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 hypovolaemia. An indwelling polyethylene catheter was placed in the femoral artery and the arterial blood pressures were measured directly by a capacitance transducer. Heart rate (HR) was determined by ECG monitoring. Partial pressure of arterial oxygen (PaO₂) and carbon dioxide (PaCO₂) as well as arterial oxygen saturation (SaO₂) were measured by ABL-510 (Radiometer, Copenhagen, Denmark). The alveolar-arterial 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 haemodynamic investigation, patients and controls underwent a mIBG myocardial scintigraphy. Briefly, after an overnight fast, 150-200 MBq of ¹²³I-metaiodobenzyl-guanidine
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(AdreView, GE Healthcare) were injected intravenously. Fifteen and 240 minutes after injection, planar and tomographical (SPECT) scintigraphy were performed by a two-headed gamma camera (Infinia, General Electric Medical Systems, Milwaukee, Wisconsin, USA), using low-energy, high-resolution collimators. In planar recordings, a matrix of 256 by 256 and acquisition time of 10 minutes 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 7x7 pixels region of interest. WOR corrected for background, was calculated as number of counts in the anterior projection at 15 minutes minus the counts at 230 minutes, the background (mediastinal) count subtracted from each count: WOR_{PI} = ((H/M of initial image – H/M of delayed image)/(H/M of initial image)) x 100% (8). The count rate at 230 minutes was corrected for radioactive decay.

Non-invasive measurements

In relation to the mIBG scintigraphy, the patients and controls underwent a non-invasive investigation of haemodynamics (blood pressure, CO, SVR, HRV, and BRS). All individuals were monitored after one hour at rest for 30 min in the supine position and after 20 min of 60° tilting. A commercially available monitoring system (Task Force Monitor® CNSystems (TFM), Graz, Austria) was used. This system integrates electrocardiogram (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 (LFsBP and LFdBP, respectively) and normalized units (LFnu-sBP and LFnu-DBP, respectively), using power spectral analysis, applying an autoregressive methodology (1;9).
Normalised as well as 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 a conventional non-computerized equipment (Megacart, Siemens-Elema, Erlangen, Germany). The QT interval was determined on the ECG (50 mm/s) as described elsewhere (13). Q-T 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 haemodynamic variables.

**Assays**

Renin concentrations were determined using a commercially available two-site immunoradiometric assay (DGR International Inc., USA). Samples were collected in ice-chilled test tubes containing aprotinin-heparin, and EDTA. The detection limit was 0.31 pg/ml and intra- and inter-assay variations were less than 2% (28). The references interval (mean±range) was 26 (5.2-33.4) pg/ml.

Plasma adrenaline and noradrenaline were analyzed by RIA using a commercial available kit (2-Cat RIA, BA-1500; from Labor Diagnostika Nord, Nordhorn, Germany), calibrated by 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 year, which may reduce the content of intact immunoactive adrenaline and
noradrenaline. However, the decrease in immunoactivity was that low, as judged on the normal
controls, that it did not influence the results.

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

Statistics

Data are presented as mean ± SD or medians and inter-quartile 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 $\chi^2$-test was used to compare proportions between groups. A p-value less than 0.05 was
considered significant.
Results

Clinical, anthropometric, biochemical, and haemodynamic 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 to controls, 10.5%, p<0.005) (Table 2 and Figure 1). Early and late H/M ratios did not significantly differ between patients and controls. In the cirrhotic patients, un-corrected WOR correlated significantly with CCT (r=-0.64, P<0.05) and QT intervals: QT (r=0.64,p<0.04), QT_c (r=0.70, p<0.02), and QT_f (r=0.71, p<0.01, Figure 2). Moreover, H/M 15 correlated significantly with pH (r=0.72, p<0.01) and H/M 230 with pH (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 left ventricle, whereas all healthy controls presented normal SPECT studies without defects (p=0.02, Figure 3). We observed no significant differences with respect to metabolic liver function, portal pressure, systemic haemodynamics, or natriuretic peptides in patients with reduced up-take compared to those with normal up-take.

Table 3 summarizes haemodynamic characteristics as assessed by TFM supine and during head-up tilt. The HR and RRI were significantly different between patients with cirrhosis and controls. HR increased further during head-up tilt both in the patients and in the controls (p<0.005). Stroke volume (SV) and the end-diastolic volume index (EDI), an estimate of left ventricular preload were significantly reduced in the cirrhotic patients (p<0.01).
Table 4 reports data on HRV. The low frequency component (LF) reflects the sympathetic nervous activity, the high frequency component (HF) the vagal innervation. LF/HF-ratio is a quantitative index of the sympathico-vagal balance and the short autonomic regulation whereas the very low frequency (VLF) component partly reflects the long-term humoral regulation. In general, we found lower LF and a higher 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 heart rate variability (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 proBNP (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 QT\textsubscript{F} (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 heart rate variability (r=0.71, p<0.01).
296 After head-up tilt HR changed significantly in both patients and controls, whereas MAP only
297 increased in the controls (p<0.001, Table 3). LF/HF increased in both patients and controls (p<0.05).
298 LF-dBP and VLF-sBP decreased in the controls after tilt (p<0.05) whereas there was no significant
299 difference in the patients (Table 4). In the controls BRS decreased (p<0.05) whereas it was unaltered
300 in the patients (Table 4).
Discussion

In this study, we attempted to evaluate autonomic nervous function by $m$IBG-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 hypovolaemia, 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 $m$IBG-uptake in cirrhosis.

$m$IBG scintigraphy has hitherto been used mainly in the management of patients with heart failure and as an important research tool (18). Recently, results of $m$IBG 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 pre-synaptic norepinephrine uptake and reduced post-synaptic beta-adrenoceptor density together with general increased sympathetic activity in the heart and in the circulation (5). This corresponds with down-regulation of myocardial beta-adrenoceptor density which is also seen both experimentally and in patients with cirrhosis (12;22). Since down-regulation of beta-adrenoceptors is seen both in patients with hypertrophic cardiomyopathy and in cirrhosis it should be considered a general non-specific 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 re-uptake and facilitation of cardiovascular response to sympathetic stimulation by the renin-angiotensin-aldosterone system (5). It should be noted that $m$IBG-scintigraphy in patients treated with beta-blockers may give
other results than in patients without medication. None of our patients were treated with beta-blockers but studies of mIBG scintigraphy in the search for responders to beta-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 (Figure 3). mIBG up-take is semi-quantified by calculating til 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 haemodynamics, 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 hypovolaemia (32). This relation lends further support to the assumption of an important link between autonomic dysfunction and development of central hypovolaemia 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 if 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 the present study most likely reflects that the abnormalities in pre-synaptic norepinephrine uptake and post-synaptic beta-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 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). But 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). A result 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 $^{123}$I-IBG uptake as obtained by $^{123}$I-IBG scintigraphy and suggest that decreased HRV is also reflected by the abnormal $^{123}$I-IBG-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 decrease in the controls during head-up tilt, no change was seen in cirrhosis after this procedure supporting impaired cardiovascular control. Decreased BRS in the cirrhotic patients furthermore correlated with H/M ratio of $^{123}$I-IBG 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 $^{123}$I-IBG 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 $^{123}$I-IBG scintigraphy would be of interest 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 $^{123}$I-IBG scintigraphy in alcoholic cirrhosis revealed autonomic and cardiac dysfunction and abnormal cardiac distribution of sympathetic activity. This seems to be associated
with central hypovolaemia, 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.
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407 References
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cirrhosis using 123I-metaiodobenzylguanidine myocardial scintigraphy and spectrum analysis of heart-rate

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**Disclosure**

No conflicts of interest are reported by any of the authors.
**Authors contributions.**

Søren Møller wrote the protocol, performed catheterisations, made data-analyses, and wrote first version of the manuscript.

Christian Mortensen included patients and participated in the catheterisations and contributed to the manuscript.

Flemming Bendtsen contributed to the protocol, to the interpretation of the results and to the manuscript.

Lars T. Jensen was responsible for the analyses of adrenaline and noradrenaline and their interpretation.

Jens P. Gøtze was responsible for the proANP and proBNP analyses and the interpretation of the results.

Jan L. Madsen were responsible for the SPECT analyses, the interpretation and contributed to the manuscript.

All authors have seen commented on, and contributed to, and approved the final version of the manuscript.
Figure legends

Figure 1. Wash-out rate, panel A and heart/mediastinum ratio in 10 patients with cirrhosis and 10 controls. bc denotes acquisition with background correction. Heart/mediastinum ratios are acquired at 15 and 230 min after injection of $^{123}$I-$m$IBG. *) p<0.005.

Figure 2. Correlations between wash-out rate (WOR) of $^{123}$I-$m$IBG and central circulation time (CCT, Panel A), QT_{F} interval (Panel B), and circulating noradrenaline concentrations (Panel C).

Figure 3. Representative polar map plots of a $^{123}$I-$m$IBG scintigraphy in a cirrhotic patient (left panel) and in a healthy control subject (right panel). The black area in the polar map plot of the cirrhotic patient represents reduced sympathetic activity in the inferior-lateral segment of the left ventricle.
### Tables

**Table 1.** Clinical, anthropometric, and biochemical characteristics of 10 patients with cirrhosis and 10 healthy controls (mean± SD). Reference interval in parentheses.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Patients</th>
<th>Controls</th>
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<tr>
<td>Height (cm)</td>
<td>171±7</td>
<td>172±14</td>
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<tr>
<td>Weight (kg)</td>
<td>69.2±15.3</td>
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<td>Gender (m/f)</td>
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<td>Age (yr)</td>
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<td>Ascites (no/yes)</td>
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<td>10/0</td>
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**Blood biochemistry**

- Blood haemoglobin (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

**Haemodynamics**

- Hepatic venous pressure gradient (mmHg; <5): 14.4±4.7
- Postsinusoidal resistance (mmHg•min•l⁻¹, <4.6): 12.3±5.5
- Right atrium pressure (mmHg, <5): 4.7±2.5
- 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•sec•cm⁻⁵): 1337±422
- Central blood volume (L): 1.47±0.28

**QT-intervals**

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<td>QTcF (ms)</td>
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### Arterial gas tensions

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<tr>
<td>Arterial O₂ tension (kPa)</td>
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<tr>
<td>Arterial O₂ saturation (%)</td>
<td>95±2</td>
</tr>
<tr>
<td>Alveolar-arterial O₂ gradient (kPa)</td>
<td>3.4±1.5</td>
</tr>
<tr>
<td>Arterial CO₂ tension (kPa)</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>Arterial standard HCO₃⁻ (meq/l)</td>
<td>24.1±2.7</td>
</tr>
</tbody>
</table>
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 (median±IQ ranges).

<table>
<thead>
<tr>
<th></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 after 15 min</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 after 230 min</td>
<td>2.05 (1.8-2.1)</td>
<td>1.90 (1.7-2.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Wash-out rate (without background correction)</td>
<td>19.5 (12.0-24.0)</td>
<td>10.5 (6.0-11.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Wash-out rate (with background correction)</td>
<td>21.0 (3.0-28.0)</td>
<td>0.0 (0.0-6.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Table 3. Haemodynamic characteristics as assessed by the TASK FORCE Monitor in 10 patients with cirrhosis and in 10 healthy controls (mean±SD).

<table>
<thead>
<tr>
<th></th>
<th>Patients with cirrhosis (n=10)</th>
<th>Controls (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Tilt</td>
</tr>
<tr>
<td>RR-Interval (ms)</td>
<td>852±147**</td>
<td>763±160**</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>73±12##</td>
<td>82±15**</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83±16</td>
<td>86±15</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>56±23##</td>
<td>48±22</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.1±1.6</td>
<td>3.8±1.4</td>
</tr>
<tr>
<td>EDI (ml/m²)</td>
<td>51±19##</td>
<td>46±19</td>
</tr>
</tbody>
</table>

*) p<0.005 vs supine position; **) p<0.001 vs supine position; #) p<0.05 vs controls; ##) p<0.01 vs controls;

MAP: Mean arterial blood pressure, EDI: End-diastolic volume index.
Table 4. Variability of heart rate and blood pressure and baroreflex sensitivity (BRS) as assessed by the TASK FORCE Monitor in 10 patients with cirrhosis and in 10 healthy controls (median and IQ ranges).

<table>
<thead>
<tr>
<th></th>
<th>Patients with cirrhosis (n=10)</th>
<th>Controls (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine Tilt</td>
<td>Supine Tilt</td>
</tr>
<tr>
<td>VLF-RRI (ms²)</td>
<td>156 (44-295)¹</td>
<td>245 (64-1432)</td>
</tr>
<tr>
<td>LF-RRI (ms²)</td>
<td>130 (56-259)</td>
<td>131 (37-258)</td>
</tr>
<tr>
<td>HF-RRI (ms²)</td>
<td>70 (33-327)</td>
<td>28 (8-380)</td>
</tr>
<tr>
<td>LF/HF-RRI</td>
<td>1.35 (0.61-2.38)</td>
<td>1.54 (0.51-6.07)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.60 (0.41-0.86)²</td>
<td>0.79 (0.56-1.98)</td>
</tr>
<tr>
<td>VLF-dBP (mmHg²)</td>
<td>1.73 (1.02-3.62)</td>
<td>0.99 (0.74-1.41)</td>
</tr>
<tr>
<td>LF-dBP (mmHg²)</td>
<td>0.9 (0.5-2.3)</td>
<td>1.1 (0.5-1.3)</td>
</tr>
<tr>
<td>HF-dBP (mmHg²)</td>
<td>1.0 (0.1-1.7)</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>LF/HF-dBP</td>
<td>1.18 (0.57-1.90)²</td>
<td>1.83 (1.02-2.71)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.60 (0.41-0.86)²</td>
<td>0.79 (0.56-1.98)</td>
</tr>
<tr>
<td>VLF-sBP (mmHg²)</td>
<td>3.1 (2.0-7.6)</td>
<td>2.5 (1.3-3.9)</td>
</tr>
<tr>
<td>LF-sBP (mmHg²)</td>
<td>1.8 (0.9-4.3)</td>
<td>1.4 (1.0-2.9)</td>
</tr>
<tr>
<td>HF-sBP (mmHg²)</td>
<td>2.7 (2.0-5.2)</td>
<td>1.1 (0.7-2.4)</td>
</tr>
<tr>
<td>LF/HF-sBP</td>
<td>0.94± (0.43-1.31)²</td>
<td>1.55 (0.84-2.16)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.51 (0.39-0.94)²</td>
<td>0.74 (0.57-1.64)</td>
</tr>
<tr>
<td>BRS slope-up (ms/mmHg)</td>
<td>10.2 (7.6-13.5)²</td>
<td>5.3 (4.7-9.2)</td>
</tr>
<tr>
<td>BRS slope down (ms/mmHg)</td>
<td>9.9 (7.3-20.1)</td>
<td>7.2 (4.6-11.6)</td>
</tr>
<tr>
<td>BRS total (ms/mmHg)</td>
<td>10.8 (7.4-15.0)²</td>
<td>6.6 (4.7-10.7)</td>
</tr>
</tbody>
</table>

* p<0.005 vs supine position; ** p<0.001 vs supine position. ° p<0.05 vs controls; °° p<0.01 vs controls. °°° p<0.05 vs controls after tilt; °°°° p<0.01 vs controls after tilt.

¹) Very low frequency (VLF) of variability of components of heart rate (RRI), diastolic blood pressure (dBP), and systolic blood pressure.

²) Low frequency (LF) of variability of components of heart rate (RRI), diastolic blood pressure (dBP), and systolic blood pressure.

²²) High frequency (HF) of variability of components of heart rate (RRI), diastolic blood pressure (dBP), and systolic blood pressure.
### Table 5. Circulating catecholamines (adrenaline and noradrenaline), renin and pro-ANP and proBNP in 10 patients with cirrhosis and 10 healthy controls (median and IQ ranges).

<table>
<thead>
<tr>
<th></th>
<th>Patients with cirrhosis (n=10)</th>
<th>Controls (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline (nmol/l)</td>
<td>0.14 (0.09-0.15)</td>
<td>0.09 (0.07-0.12)</td>
<td>Ns</td>
</tr>
<tr>
<td>Noradrenaline (nmol/l)</td>
<td>1.90 (1.54-2.40)</td>
<td>2.22 (1.39-2.99)</td>
<td>Ns</td>
</tr>
<tr>
<td>Renin (ng/l)</td>
<td>12.5 (6-37)</td>
<td>9.5 (6-13)</td>
<td>Ns</td>
</tr>
<tr>
<td>ProANP (pmol/l)</td>
<td>127.7 (98.9-150.6)</td>
<td>53.4 (43.6-74.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ProBNP (pmol/l)</td>
<td>13.8 (9.8-22.8)</td>
<td>3.1 (2.4-5.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 1

A

Wash-out rate (%)

Cirrhosis Controls Cirrhosis_{bc} Controls_{bc}

B

Heart/mediastinum ratio

Cirrhosis_{15 min} Controls_{15 min} Cirrhosis_{230 min} Controls_{230 min}
Figure 2

A

B

C

\[ r = -0.64, \ p < 0.05 \]

\[ r = -0.71, \ p < 0.01 \]

\[ r = 0.77, \ p < 0.01 \]
Figure 3

Cirrhosis  Control