Autonomic dysfunction in alcoholic cirrhosis and its relation to sudden cardiac death risk predictors

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Abstract. Patients with liver cirrhosis have autonomic dysfunction and complex cardiovascular changes. Increases risk for sudden cardiac death (SCD) was recently recognized in liver cirrhosis. This study analyzed risk predictors for SCD related to autonomic dysfunction in patients with alcoholic liver cirrhosis (ALC). Twenty five patients with ALC were examined and compared with healthy control group. Cardiovascular autonomic reflex tests, comprehensive ECG with QTc interval, late potentials, short-term heart rate variability (HRV) analysis (time domain, spectral and nonlinear-Poincare plot analysis) and 24-h Holter ECG with long-term HRV analysis were done. According to autonomic reflex tests patients with ALC had high incidence (56%) of severe autonomic dysfunction, manifested as pronounced damage of vagal function. Patients had significantly depressed HRV (SDNN, SDANN, triangular index, LF and HF) and more frequently had serious arrhythmias, prolonged QTc and Poincare plot in a shape of dot ($p < 0.001$). In patient group QTc significantly inversely correlated with spectral components from short-term HRV analysis (ln(LF): $r = -0.53$, ln(HF): $r = -0.47$; $p < 0.05$), and Lown class significantly correlated with total autonomic function score ($r = 0.64$, $p = 0.04$). This study indicates that in ALC autonomic neuropathy with vagal impairment and sympathetic predominance is related to SCD risk predictors and onset of serious ventricular arrhythmias.

Key words: Autonomic function — Alcoholic cirrhosis — Sudden cardiac death

Introduction

Liver cirrhosis is associated with complex cardiovascular changes, including hyperdynamic circulation with increased blood volume, increased cardiac output and reduced peripheral vascular resistance (Møller and Henriksen 2008). Autonomic dysfunction is common in liver cirrhosis, both in alcoholic and non-alcoholic and is associated with the severity of hepatic dysfunction (Dillon et al. 1994; Ates et al. 2006) and survival (Hendrickse et al. 1992; Fleckenstein et al. 1996). The pathogenesis of autonomic neuropathy in cirrhosis is not fully known and several mechanisms are suggested: circulatory changes in cirrhosis, metabolic and neurohormonal alterations including renin angiotensin aldosterone system, excessive nitric oxide production, oxidative stress and inflammatory mediators (interleukines) (Møller and Henriksen 2008). Autonomic dysfunction in cirrhotic patients has been evaluated by standard autonomic function test (Gonzalez-Reimers et al. 1991; Dillon et al. 1994; Szalay et al. 1998), heart rate variability (HRV) (Dillon et al. 1994; Fleisher et al. 2000; Ates et al. 2006) and 123I-metaiodobenzylguanidine myocardial scintigraphy (Iga et al. 2003). According to standard autonomic function tests, autonomic neuropathy in liver cirrhosis is characterized with predominately vagal impairment (Hendrickse et al. 1992; Dillon et al. 1994; Ates et al. 2006). Cirrhotic patients with

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vagal neuropathy have a five-fold increased mortality compared to those without autonomic dysfunction (Hendrickse et al. 1992; Fleckenstein et al. 1996). However, mechanisms behind increased mortality related to autonomic dysfunction have not been evaluated. Recently, in patients with primary biliary cirrhosis unexplained excess mortality that remains even after accounting for liver and cancer-related deaths was recognized and potentially linked to increased risk of sudden cardiac death (SCD) (Newton et al. 2006).

Conversely, incidence of SCD is increased in chronic alcoholics (Moushmoush and Mansour 1991; Hémery et al. 2000; Spies et al. 2001). Chronic alcohol ingestion induces autonomic neuropathy, predominately of vagal origin (Duncan et al. 1980; Matikainen et al. 1986; Barter and Tanner 1987), potentially contributing to increased incidence of SCD in alcoholics (Yokoyama et al. 1992; Johnson and Robinson 1998), apart from heart muscle disease (alcoholic cardiomyopathy) often seen with chronic alcohol abuse.

Therefore, patients with alcoholic etiology of cirrhosis, at least from pathophysiological background, could be at increased risk of SCD. Autonomic dysfunction induced both by metabolic and homodynamic changes in cirrhosis and alcohol ingestion itself, could contribute to increased risk of SCD.

This study was aimed to evaluate presence and level of autonomic dysfunction in patients with alcoholic cirrhosis by standard cardiovascular autonomic function tests and to analyze risk predictors for sudden cardiac death related to autonomic dysfunction (HRV, late potentials and QTc interval).

Materials and Methods

Study population

The study was carried out on 25 patients with alcoholic hepatic cirrhosis and 17 healthy individuals similar in age and sex. Twenty five consecutive patients with previously proven liver cirrhosis and with the history of at least ten years of ethyl consumption more than 80 g per day were enrolled in this study. The diagnosis of cirrhosis was made histopathologically or based on clinical examination, laboratory parameters, ultrasonographic findings, and the presence of esophageal varices. Patients were admitted to Department of Gastroenterology of Clinical and Hospital Center "Bezanijska Kosa" for the further treatment (basic clinical data are shown in Table 1). Exclusion criteria were: coronary disease, heart failure, diabetes, chronic obstructive pulmonary disease and therapy with drug(s) known to influence autonomic function. The controls were healthy volunteers with no history of alcohol consumption and normal clinical and biochemical parameters. The study was approved by the Scientific Ethical Committee of Clinical Hospital Center "Bezanijska Kosa". Written informed consent was obtained from all subjects.

Table 1. Group characteristics

Alcoholics	$n = 25$
Gender (M/F)	20/5
Age (years, range)	54 (46–62)
EF (%)	58 ± 13
ESV (ml)	47 ± 11
EDV (ml)	117 ± 37
Control group	$n = 19$
Gender (M/F)	15/4
Age (years, range)	52 (44–60)

EF, ejection fraction; ESV, end systolic volume; EDV, end diastolic volume by 2D echocardiography.

Study protocol

All individuals were tested in the Neurocardiology Laboratory using the original protocol for the assessment of autonomic nervous system function and cardiovascular risk parameters related to cardiac death. Cardiovascular reflex tests were done first, followed by short-term ECG recording (10 min) with statistical, spectral and nonlinear (Poincare plot) analysis of HRV as well as late potentials analysis. Individuals were tested between 09:00 and 10:00 a.m., approximately 2 h after light breakfast, under ideal temperature conditions (23°C), without any previous consumption of alcohol, nicotine or coffee. In patients therapy was withdrawn 24 h before testing. After initial testing, at the same day 24-h Holter ECG was started and day after 24-h ambulatory blood pressure (BP) monitoring was done.

Cardiovascular reflex tests

We performed three parasympathetic tests (heart rate response to Valsalva maneuver, heart rate response to deep breathing and heart rate response to standing) and one test of sympathetic function (BP response to standing).

Heart rate response to Valsalva maneuver

Valsalva maneuver was performed using modified sphygmomanometer with blowing and holding a pressure of 40 mmHg for 15 s, with ECG recording. The results, expressed as a Valsalva ratio, measured the longest and the shortest RR interval using ruler and ECG trace.

Deep breathing test

Six deep inspirations and expirations were performed over one minute. The result is expressed as a difference between the highest and the lowest heart rate.

Heart rate response to standing test (30 : 15 ratio test)

Heart rate response after standing, expressed as a ratio between the longest RR interval corresponding with 30th beat after starting and the shortest RR interval corresponding with 15th beat.

BP response to standing

This test measured the subject's BP with a sphygmomanometer while he was lying quietly and one minute after he was made to stand up. The postural fall in BP was taken as the difference between the systolic pressure lying and the systolic BP standing.

Results of all four tests were expressed as a normal, borderline or abnormal, according to cut-off values given by Ewing and Clarke 1982). The patients were categorized as normal, if none of the tests was abnormal; with early parasympathetic damage, if results of one of the three tests of parasympathetic function was abnormal; with definite parasympathetic damage, if two or more of the three tests of parasympathetic function were abnormal; and with combined damage, if test of the sympathetic function was abnormal in addition to parasympathetic damage. For the purpose of the above-mentioned classification the borderline tests were interpreted as normal. A scoring system like the one suggested by Bellavere et al. (1983) was also used to assess the extent of autonomic nervous damage. For each test "0" score was given for normal, "1" for borderline, and "2" for an abnormal value. By adding the score of each of the five standard tests of autonomic function, total autonomic function score was determined for every subject.

Short-term ECG and short-term HRV analysis

Analysis of standard 12 leads ECG recording using commercially available softer (Schiller model AT-10, Austria) include ECG waves and interval analysis: duration of P wave, PQ interval, QRS complex, QT and QTc interval.

QT parameters were measured automatically from the 12-lead ECG recording (Schiller model AT-10, Austria) at a paper speed of 50 mm/s (gain, 10 mm/mV). The QT interval was measured from the onset of QRS complex to the end of T wave. Each QT interval was corrected for patient heart rate according to Bazett's formula: QTc = QT/$\sqrt{}$ (RR interval), where QT and RR interval are expressed in seconds.

Short-term HRV analysis was done from 512 consecutive RR intervals using commercial softer (Schiller model AT-10, Austria) according to previously published guideline (see in References: Task Force of the ESC 1996). Short-term HRV analysis includes: time domain analysis, frequency domain analysis and nonlinear HRV analysis (Poincare space plot). The following time domain variables were computed for each subject: average dRR interval, standard deviation of dRR intervals (SDRR), mean deviation of dRR (MDRR), square root of the mean of squared differences of two consecutive RR intervals (RMSSD), percent of beats with consecutive RR interval difference of more than 50 ms (pNN50). The following short-term frequency domain indices were determined using Hanning window type signal limitation before Fourier transformation: very low-frequency (VLF, 0.016–0.05 Hz), low-frequency (LF, 0.05–0.15 Hz), high-frequency (HF, 0.15–0.35 Hz) power, and LF/HF ratio. Late potential analysis was done based on data obtained from 12 standard ECG leads. Criteria for the presence of late potentials (frequency range of 40 to 250 Hz) were as follow: QRS duration >114 ms, LAHFd >38 ms, RMS-40 ms <20. In the presence of at least two parameters, late potential concerned as was positive. Nonlinear analysis (Poincare space plot): results of nonlinear Poincare space plot analysis were divided related to visual form (cigarette, cluster, comet or spot).

Holter ECG: rhythm analysis and long-term HRV analysis

24-h ambulatory ECG recordings were acquired by 3 leads ECG, sampling rate 1000 Hz per each lead (Biosensor, USA) and analyzed by an experienced analyst. Cardiac rhythms were screened for ventricular premature beats and supraventricular premature beats. The recordings were reviewed, and the beat classifications were manually checked, corrected, and readied for further analysis. After all of the artifacts and misclassified beats were corrected, time and frequency domain HRV analysis were carried out using the software package present in the system. The fast Fourier transformation and Hanning window were used for the analysis of the frequency (spectral) domain parameters.

In rhythm analysis total number of ventricular premature beats and supra ventricular premature beats for the whole period of recording was determined and number of ventricular premature beats per hour calculated. Also, the degree of arrhythmias was quantified according to Lown classification.

From time domain HRV analysis following time domain variables were computed: mean RR interval for 24 h (mean NN), standard deviation of normal RR intervals (SDNN), standard deviation of all 5-min mean normal RR intervals (SDANN), square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD). From frequency domain HRV analysis following 24-h frequency domain indices were determined: total power (TP, 0–0.4 Hz), HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), and the (LF/HF ratio). Heart rate is measured in milliseconds; variance, which is referred to as the power in a portion of the total spectrum of frequencies, is measured in milliseconds squared. Triangular index was also determined from 24-h HRV analysis according to guidelines (Task Force of the ESC 1996 – see in References).

24-h ambulatory BP monitoring

Evaluation of 24 h profile of BP was done using recorder and commercial software for analysis (Mobil-O-graph). Monitoring began at approximately 11 a.m. and BP measurements were performed by oscillometric method every 15 min all day long. From these data following variables were calculated for each patient: average total (24 h), daytime (9 a.m.–9 p.m.) and nighttime (0 a.m.–6 a.m.) systolic BP, diastolic BP and pulls pressure; systolic and diastolic BP variability during day and during night expressed as standard deviation of all systolic and all diastolic BP measurements during daytime and during night (automatically calculated using the same software).

Statistics

All data were analyzed using computer software package SPSS 11.05 system for Windows. Beside the measures of the central tendency, parametric data were analyzed using independent *t*-test and Pearson chi-square (χ^2) test. Significance level was defined as $p < 0.05$. Since all components of HRV do not have normal distribution, ln transformation was done and parametric statistics applied afterward. Correlations between variables were tested using Pearson's coefficient.

Results

Cardiovascular reflex tests

Cardiovascular reflex tests were done in 16 out of 25 patients and in all controls. Parasympathetic dysfunction was present in 14/16 (87%) patients with alcoholic cirrhosis: seven patients (43%) have early and seven patients (43%) definitive parasympathetic damage. The result of Valsalva maneuver was abnormal in 5 patients, deep breathing test was abnormal in 9 patients and heart rate response on standing was abnormal also in 9 patients. Sympathetic dysfunction, manifested as orthostatic hypotension, was present in only 3 patients and only one of them did not have parasympathetic damage while rest two have parasympathetic dysfunction. Combined damage, parasympathetic and sympathetic dysfunction, was diagnosed in 2/16 (12.5%) patients. As expected, pathological results of cardiovascular reflex test were more common among patients with alcoholic liver diseases compared to control (Fig. 1). Total autonomic function score was higher in patients compared to control (4.70 ± 1.70 vs. 2.05 ± 1.50, $p < 0.001$) and nine out of sixteen patients (56%) have severe autonomic dysfunction (score >7) (Table 2).

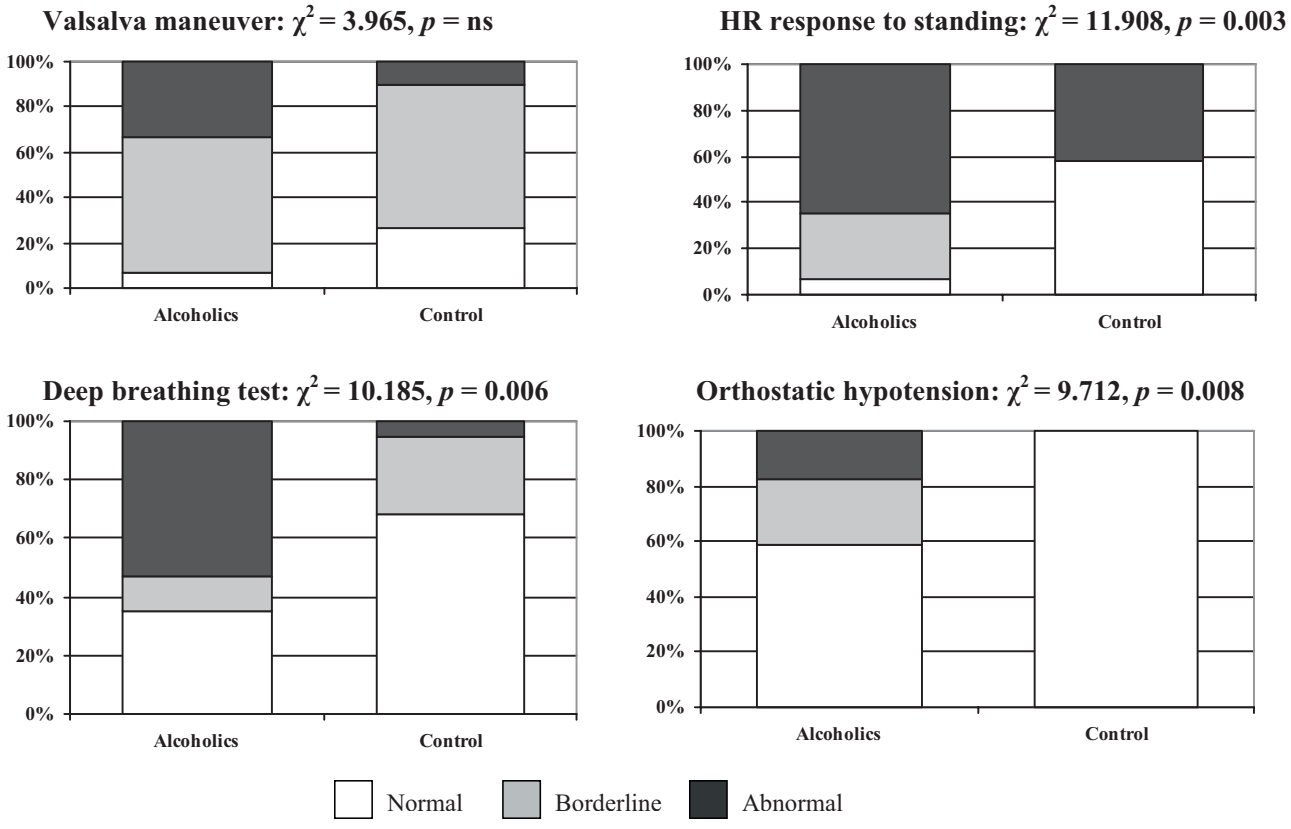

Figure 1. Cardiovascular reflex tests.

Table 2.

A. Distribution of autonomic dysfunction among alcoholics and control

	Parasympathetic damage			Sympathetic damage	Combined damage
	Without	Early	Definitive		
Alcoholics (n = 16)	2	7	7	3	2
Control (n = 19)	9	9	1	0	0

For parasympathetic damage: $\chi^2 = 9.014$, $p = 0.011$.

B. Extent of autonomic nervous damage based on total autonomic function score

	Autonomic nervous damage (autonomic neuropathy)			
	Without (0–1)	Mild (2–3)	Moderate (4–6)	Severe (7–10)
Alcoholics (n = 16)	0	1	6	9
Control (n = 19)	4	6	9	0

$\chi^2 = 17.039$, $p = 0.001$.

C. Distribution of autonomic dysfunction among alcoholics (n = 16)

		Parasympathetic damage			Total
		Without	Early	Definitive	
Sympathetic damage	Without	1	6	6	13
	With	1	1	1	3
Total		2	7	7	16

QT interval

The analysis of the QTc interval showed that it was significantly longer in patients with alcoholic liver disease, compared to healthy individuals (454.06 ± 25.33 vs. 419.72 ± 19.432 ms, $p < 0.001$). No significant difference was found between groups concerning duration of non-corrected QT interval, PQ interval, QRS complex and P wave. Prolonged QT (QTc > 440 ms) was present in 13/25 patients (52%) that is significantly more frequent compared to control group where only 3/19 individuals (6%) have prolonged QTc ($\chi^2 = 5.46$, $p = 0.026$).

Short-term HRV analysis

All spectral and time domain parameters were considerably lower in alcoholics. Values of RMSSD and HF reflecting vagal activity were significantly depressed in patients with alcoholic liver disease. LF spectral parameter reflecting sympathetic and vagal function was also lower in patients with the liver cirrhosis. LF/HF ratio, reflecting sympathovagal balance, was higher in alcoholics compared to control suggesting, however without statistical significance (Table 3).

Table 3. Short-term heart rate variability analysis

	Alcoholics	Control group	p
Average dRR (ms)	8.50 ± 8.78	25.22 ± 16.69	0.001
SDRR (ms)	8.56 ± 8.83	22.22 ± 12.54	0.001
MDRR (ms)	5.43 ± 5.36	16.33 ± 10.31	0.001
pNN50 (%)	1.43 ± 3.36	8.16 ± 9.90	0.014
RMSSD (ms)	12.37 ± 12.26	32.88 ± 21.36	0.002
ln(VLF)	3.60 ± 1.49	4.93 ± 1.13	0.007
ln(LF)	3.28 ± 1.40	4.81 ± 1.05	0.001
ln(HF)	2.26 ± 1.45	3.89 ± 1.26	0.002
LF/HF	5.02 ± 3.73	3.78 ± 3.64	n.s.

SDRR, standard deviation of dRR intervals; MDRR, mean deviation of dRR; RMSSD, square root of the mean of squared differences of two consecutive RR intervals; pNN50, percent of beats with consecutive RR interval difference of more than 50 ms; VLF, very low-frequency interval (0.016–0.05 Hz); LF, low-frequency interval (0.05–0.15 Hz); HF, high-frequency interval (0.15–0.35 Hz); n.s., non-significant.

Late potentials

Late potentials were positive only in one patient with alcoholic cirrhosis.

Nonlinear HRV analysis

Poincare plot in the shape of dot, indicating severe autonomic dysfunction, was present in 9/25 patients, 5/25 patients have Poincare plot in comet form and 11/25 in cigarette form. None of patients have Poincare plot in cluster form. In control group Poincare plot in dot for was not registered, 8/19 individuals have Poincare plot in cluster form, 10/19 in comet form and only 1/19 in cigarette form (for comparison between patients vs. control: $\chi^2 = 24.8$, $p < 0.001$).

Long-term HRV and arrhythmia analysis from 24 h

Analysis of time domain parameters indicated statistical significance for three important arrhythmia risk predictors. The SDNN, SDANN and triangular index had considerably lower values in alcoholics when compared to the control group. Power spectral analysis of long-term HRV revealed lower both ln(LF) and ln(HF). Supraventricular and ventricular premature beats were more common in alcoholics (Table 4).

Arrhythmia analysis from 24-h ECG monitoring revealed significantly different distribution according to Lown class between patients with alcoholic cirrhosis vs. control ($p = 0.011$). Among patients serious ventricular rhythm abnormalities (Lown class >2) were present in 10/25 (39%) patients, 12/25 (46%) patients were in Lown class 1 and 3/25 (15%) in Lown class 0. In control group 15/19 (76%) individuals have Lown class 0, 3/19 (16%) Lown class 1 and 1/19 (8%) person has Lown class >2.

Table 4. 24 h Holter ECG: long-term HRV analysis

	Alcoholics	Control group	*p*
VPB	758.3 ± 502.2	23.5 ± 20.3	0.04
SVPB	85.2 ± 38.1	4.4 ± 1.9	0.05
Mean RR (ms)	712.21 ± 157.00	782.76 ± 77.84	n.s.
SDNN (ms)	93.42 ± 42.69	463.15 ± 111.83	0.014
SDANN (ms)	71.80 ± 43.38	187.53 ± 85.74	0.000
RMSSD (ms)	53.00 ± 36.32	70.38 ± 30.78	n.s.
TRI INDEX	33.71 ± 17.17	50.61 ± 9.70	0.005
LF/HF	3.40 ± 2.11	3.55 ± 1.13	n.s.
ln(LF/HF)	0.99 ± 0.75	1.22 ± 0.30	n.s.
ln(LF)	6.85 ± 0.94	8.19 ± 0.98	0.002
ln(HF)	5.81 ± 1.17	7.00 ± 0.99	0.009

VPB, total number of ventricular premature beats during ECG monitoring; SPB, total number of supraventricular premature beats during ECG monitoring; SDNN, standard deviation of all the RR intervals; SDANN, standard deviation of all 5-min mean normal RR intervals; RMSSD, square root of the mean of squared differences of two consecutive RR intervals; TRI INDEX, triangular index; VLF, very low-frequency interval (0.016–0.05 Hz); LF, low-frequency interval (0.05–0.15 Hz); HF, high frequency interval (0.15–0.35 Hz); n.s., non-significant.

Correlations between autonomic function, repolarization abnormalities and arrhythmias in patients with alcoholic cirrhosis

In patients with alcoholic cirrhosis QTc significantly inversely correlated with spectral components from short-term HRV analysis: ln(LF) ($r = -0.53$, $p = 0.03$) and ln(HF) ($r = -0.47$, $p = 0.04$). We did not find significant correlation between HRV parameters from long-term HRV analysis and Lown class. In 16 patients in whom standard cardiovascular reflex tests were done Lown class significantly correlated with total autonomic function score ($r = 0.64$, $p = 0.04$).

Ambulatory BP monitoring

Detailed ambulatory BP analysis during 24 h including mean systolic and mean diastolic BP during 24 h, daytime, night-time, early in the morning, as well as systolic and diastolic BP variability, did not reveal statistically significant differences between patients with alcoholic cirrhosis and control.

Discussion

Autonomic dysfunction assessed by standard autonomic function tests in alcoholic cirrhosis

This study confirms that high percent of patients with alcoholic cirrhosis has abnormal autonomic function. In the current study in 16 out of 25 consecutive patients with alcoholic liver cirrhosis admitted to the hospital for further medical treatment, standard autonomic function tests were performed with satisfied patient's compliance and in more than 80% of these patients at least one or more parasympathetic function test was abnormal. Damage in sympathetic function was detected in lower percent. According to total autonomic function score 56% of evaluated patients in the current study have severe autonomic damage, comparable to findings of Fleckenstein et al. (1996).

Incidence of autonomic neuropathy based on traditional autonomic function test widely varies in chronic liver disease: from as low as 35% (Hendrickse and Triger 1990) to 45% (Hendrickse et al. 1992), 60% (Dillon et al. 1994) or even 80% (Bajaj et al. 2003). Higher frequency of neuropathy was found in studies involved higher proportion of patients with severe form of hepatic failure (80%) (Bajaj et al. 2003), compared to studies recruited patients with mild hepatic impairment (45%) (Hendrickse et al.1992). Cardiovascular autonomic dysfunction is significantly more frequent in

advanced liver disease compared with early liver disease (Hendrickse et al. 1992).

Using standard cardiovascular tests we, as others, found predominately vagal impairment in chronic alcoholic liver disease. Importance of vagal impairment for sodium and fluid retention has been shown in cirrhosis (Hendrickse and Triger 1994; Dillon et al. 1997; Trevisani et al. 1999). Neuromodulation with angiotensin II is proposed as one of the mechanism inducing parasympathetic dysfunction in cirrhosis and partly correction of vagal dysfunction in cirrhotic patients was achieved by captopril (Dillon et al. 1997).

In our study heart rate response to standing was the most frequently abnormal test. Barter and Tanner (1987) in their study also reported heart rate response to standing as the most sensitive test with high specificity, as well as Bajaj et al. (2003). Impaired cardiac and circulatory (BP) responses to orthostasis in cirrhosis are probably due to blunted baroreflex function (Laffi et al. 1997; La Villa et al. 2002; Newton et al. 2006). Impaired baroreflex function in cirrhosis can be related to activated renin angiotensin aldosterone system, since administration of canrenone, an aldosteron antagonist, in compensated cirrhotic patients normalizes cardiac response to postural changes (La Villa et al. 2002).

Clinical significance of vagal neuropathy detected by standard tests in liver cirrhosis is important. A strong correlation between the number of abnormal test and Child-Pugh score was demonstrated implying that with disease progression cardiovascular autonomic impairment also progress. In multiple regression analysis presence of vagal neuropathy in liver cirrhosis detected by standard autonomic tests is independent predictor of mortality (Hendrickse et al. 1992).

HRV in alcoholic cirrhosis

Cardiovascular reflex tests are relatively simple and useful to classify patients for the presence of autonomic neuropathy and its severity, but HRV potentially offers better accuracy (Malpas et al. 1991; Dillon et al. 1994) and is less dependent of patient compliance. Alcoholics without manifest cardiac disease have considerably lower HRV compared to control, even in cases with normal standard autonomic tests (Malpas et al. 1991). Malpas show that in chronic alcoholics SDSD index from statistical analysis of 24-h HRV (corresponding to HF from spectral analysis) can detect small changes in autonomic function, which may not be detectable by standard autonomic function test (Malpas et al. 1991).

In our study we could perform autonomic test in 16 out of 25 patients, because in the rest 9 patients adequate compliance was not achieved. However, HRV analysis was done in all, independently of patient condition, suggesting that in clinical practice HRV analysis is more feasible and applicable for autonomic function assessment than standard reflex tests.

In the present study we performed both short- and long-term HRV analysis, both time and frequency domain. By short-term HRV analysis in rest, we confirmed that patients with alcohol cirrhosis compared to control have decreased all time domain parameters (average dRR, SDRR, MDRR, RMSSD and pNN50). We also found that patients have all spectral components detected by short-term spectral analysis (VLF, LF and HF) significantly reduced compared to control, with trend towards increased LF/HF ratio. These results demonstrate impaired autonomic function in alcoholic cirrhosis with trend towards the sympathetic predominance. Fleisher et al. (2000) in patients awaiting liver transplantation found by short-term HRV analysis depressed SDNN, pNN50 (marker of parasympathetic activity) and ApEn (approximate entropy, a measure of regularity). During follow up ApEn was significantly lower in no survivors than in survivors. Iga et al. (2003) using spectral analysis of HRV shown that autonomic abnormalities appear early in the course of liver cirrhosis and that with progression of hepatic impairment LF/HF ratio increases, as well as blood level of norepinephrine, whereas HF power decreased.

Poincare plot offers exploration of non-linear phenomena involved in the genesis of HRV (Carrasco and Gaitan 2001; Piskorski and Guzik 2007). It is used for cardiac autonomic assessment and risk stratification in heart failure (Voss et al. 2007) and myocardial infarction (Milovanović et al. 2007). To the best of our knowledge there are no published data, related to the form of Poincare plot in alcoholics or in patients with alcoholic cirrhosis. In the present study we used visual analysis of the spatial form of Poincare plot and in 36% of patients found the dot shape. Dot shape of Poincare plot was previously shown to correspond with severe autonomic dysfunction and poor prognosis after myocardial infarction (Milovanović et al. 2007).

In the present study long-term time domain HRV analysis revealed in patients with alcoholic cirrhosis significantly reduced SDNN and SDANN parameters compared to the control. Ates et al. (2006) shown that severity of cirrhosis expressed using Child-Pugh classification scores is associated with reduced timed domain HRV measurements from 24-h ECG and that HRV was significantly lower in nonsurvivors than in survivors, suggesting prognostic significance of long-term time domain HRV analysis. Cooelho et al. (2001) found interesting positive correlations between SDNN and protrombin activity as well as with serum albumin but not with total bilirubin, indicating that autonomic dysfunction in liver cirrhosis is more closely related to hepatocellular dysfunction than cholestasis.

Triangular index is HRV parameter from geometric method and express overall HRV measured over 24 h. It was shown to be important prognostic marker for risk stratification after myocardial infarction (Kleiger et al. 1987), but has not been evaluated in liver cirrhosis. In the present study

we for the first time found in cirrhotic patients reduced triangular index. Prognostic value of HRV triangular index in cirrhosis remains to be determined.

The spectral analysis of long-term HRV assessment in the present study revealed significantly reduced both LF and HF component in cirrhotic patients compared to control, however, without significant difference in LF/HF ratio. Coelho et al. (2001) also reported in patients with cirrhosis decreased average total power with reduction of all components (VLF, LF, HF) in the absence of significant difference in LF/HF ratio. This spectral profile is characteristic for conditions with increased sympathetic activity and vagal impairment. Increased sympathetic activity in cirrhosis is demonstrated also by increased burst frequency and increased circulating cathecholamines and is in direct relation to the severity of the disease (Henriksen et al. 1998). The major triggers of the sympathetic overactivity seems to be baroreceptor- mediated stimulation, owing to the low arterial BP and hepatic dysfunction and a volume receptor mediated stimulation, owing to reduced central and arterial blood volume. Consequences of increased sympathetic activity in cirrhosis are important. Enhanced sympathetic tone with increased cellular exposure to noradrenalin for longer periods cause myocardial injury and impaired β adrenergic function (Opie 1998) with down regulation of β adrenergic receptor in cardiomyocytes and receptor desensitization with post receptor defects (Ma and Lee 1996), leading to cardiac dysfunction in liver cirrhosis (Møller and Henriksen 2002).

Arrhythmias in alcoholic liver cirrhosis and its correlation with autonomic disturbances

There is little data in literature regarding rhythm disturbances in patients with cirrhosis. The vast data are from case reports regarding ventricular arrhythmias, frequently torsade de points, occurs during or after liver transplantation (Lustik et al. 1998; Zaballos et al. 2005). The development of atrial fibrillation as well as episodes of supraventricular and ventricular tachycardia and even bradicardia associated with liver transplantation has also been described. There are several risk factors for arrhythmia and altered cardiac conduction in this specific situation: severe haemodynamic alterations, ion imbalance (hypokalemia, hypomagnesaemia), acid-base imbalance and hypothermia that accompany the reperfusion of a new organ.

In the present study in patients with severe, chronic alcoholic cirrhosis we found increased ectopic cardiac activity. Serious ventricular arrhythmias (Lown class >2) were present in 39% of patients and Lown class significantly correlated with total autonomic function score.

Several lines of evidence suggest that heavy drinking increase the risk of SCD with fatal arrhythmia as the most likely mechanism (Hémery et al. 2000; Spies et al. 2001; Newton et al. 2006). Although heart muscle disease induced by alcohol cardiotoxicity, i.e. alcoholic cardiomyopathy (clinically manifest or occult) is important arrhythmogenic substrate in chronic alcoholics, alcoholic autonomic neuropathy is at least contributing factor. In cirrhosis, independent of its etiology, fluidity of the plasma membrane and the function of membrane ion channels are impaired (Liu and Lee 1999). Electrophysiological abnormalities in cardiac excitation due to alteration in K^+ and Ca^{2+} channels were suggested that could potentially lead to serious ventricular arrhythmias (Moreau et al. 1994; Moreau and Lebrec 1995). However, link between cirrhotic autonomic neuropathy and cardiac rhythm disturbances was not evaluated.

In current study we found significant positive correlation between Lown class and total autonomic function score, robust index of global autonomic function, indicate potential association between ventricular arrhythmias and autonomic neuropathy. It should be noted that many other factors such as ion imbalance, and acid-base imbalance frequently present in advanced cirrhosis could be also potential proarrhythmogenic factors. Also, increased level of circulating cathecholamines could act as proarrhythmogenic agent. However, in the recent experimental study in cirrhotic rats reduced susceptibility to epinephrine-induced arrhythmias was shown and linked to potential protective effects of long-term NO overproduction (Tavakoli et al. 2007).

Prolonged QT interval in alcoholic cirrhosis and its relation with autonomic disturbances

In the present study QTc interval was much longer in cirrhotic patients compared to control and QTc > 440 ms was present in 52% of patients. A prolonged QTc interval has been previously described in 30–60% of patients with liver disease (Ishizaki et al. 1995; Mohamed et al.1996; Bal and Thuluvath 2003). Etiology of prolonged QTc in liver diseases is still unsettled. Ward et al. (1997) have shown decrease K^+ currents in ventricular cardiomyocytes from cirrhotic rats, which prolong the repolarization time and consequently QT interval (Day et al. 1993). The prolonged QTc interval could trigger sever ventricular arrhythmias, especially torsade de point and sudden cardiac death, but evidences from clinical studies are sparse. In cirrhotic patients the prolonged QT interval is significantly related to the severity of the liver disease, portal hypertension, portosystemic shunts, elevated BNP and proBNP, elevated plasma noradrenaline and reduced survival (Møller et al. 2002). The prolongation of QT interval is partly reversible after liver transplantation (Ward et al. 1997) and β-blocker treatment (Møller et al. 2002). We as well as Puthumana and co-workers could not find significant association between autonomic cardiovascular reflexes and QTc (Puthumana et al. 2001). However, we did found significant inverse correlation between duration of

QTc interval with LF and HF power spectral component. Since HRV is in some aspects more sensitive than standard autonomic cardiovascular tests, association between spectral components of HRV and QTc interval duration could suggest that autonomic dysfunction in alcoholic cirrhosis has some potential influence on delayed repolarization process in the myocardium. Also, in several studies QTc correlated with blood noradrenaline level confirming further association between autonomic function and QTc duration, as well as observation that QT is normalized with chronic β-blocker treatment in patients with prolonged baseline values (Zambruni et al. 2008). The importance of prolonged QTc interval in liver disease as independent prognostic parameter is still uncertain (Mohamed et al. 1996). Recently, QT dispersion and corrected QT dispersion parameters are suggested in to be better mortality indicators than QT intervals (Kosar et al. 2007).

Ambulatory BP recordings in cirrhotic patients

BP depends on cardiac output and the systemic vascular resistance.

Although total blood volume is increased in cirrhosis, as well as cardiac output, significant low systemic vascular resistance (arteriolar vasodilatation) with increased total vascular and arterial compliance maintain BP in low normal or even hypotensive range. There is a growing body of evidence that systemic nitric oxide over production in cirrhosis play a major role in the arteriolar and splanchnic vasodilatation and vascular hyporeactivity. However, in the present study using 24-h ambulatory BP monitoring we did not found significant difference in 24-h BP profile in cirrhotic patients compared to healthy individuals. Møller et al. (1995) report that arterial BP is reduced during the day, whereas at night the values are normal, indicating an abnormal BP regulation in cirrhosis.

It should be noted that new entity "cirrhotic cardiomyopathy" has been introduced recently (Møller and Henriksen 2008). According to this concept, patients with liver cirrhosis due to complex modifications of circulation, neurohormonal and metabolic changes have altered cardiac function. Cirrhotic cardiomyopathy is chronic cardiac dysfunction in cirrhotic patients characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation, with electrophysiological abnormalities in the absence of other known cardiac disease (Møller et al. 2008). Heart rhythm and conduction disturbances as well as altered cardiovascular autonomic function in liver cirrhosis are considered to be a part of this complex entity. In the present study exclusion and inclusion criteria were not defined to include or exclude patients with cirrhotic cardiomyopathy, according to suggested diagnostic criteria. We did not include patents with over heart failure and patients with depressed ejection fraction by echocardiography. However, presence of some aspects of cirrhotic cardiomyopathy cannot be rolled out in the current study population.

Study limitation

The current study was performed on relatively small number of patients and in some of them classic cardiovascular autonomic function tests could not be performed with satisfied patient compliance, predominately due to patient's poor general condition. This could represent potential selection bias regarding analysis of autonomic function based on classical function tests, but at the same time represent limited feasibility of standard test when they are applied on severely ill patients. However, in the present study even on smaller number of relatively clinically better-preserved patients, we found severe form of autonomic dysfunction in high percent of patients.

In the present study we did not investigate links and associations between autonomic dysfunction and liver functional status, because it was not the aim of the current study.

Conclusion

Patients with alcoholic liver cirrhosis, according to the present study, have a severe form of autonomic dysfunction, manifested as more pronounced damage of vagal function and sympathetic predominance. Analysis of cardiovascular risk for the onset of sudden cardiac death revealed presence of several potentially important risk predictors, such as decreased SDNN value, Poincare plot in shape as dot, lower triangular index, serious arrhythmias, and prolonged QTc interval. Lown class and QTc interval are shown to be associated with the level of autonomic dysfunction. However, prognostic values of these risk predictors and their links to autonomic neuropathy in patients with liver cirrhosis are still to be firmly evaluated in longitudinal and larger studies.

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