Assessment of autonomic dysfunctions in patients with non-cirrhotic portal fibrosis

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ABSTRACT

Introduction and Aim: Autonomic dysfunction has been observed in both alcoholic and nonalcoholic chronic liver diseases. Autonomic (both parasympathetic and sympathetic) functions are affected in these diseases. However, there are few studies on autonomic dysfunctions in non-cirrhotic portal fibrosis (NCPF) compared with cirrhosis. Therefore, in the present study we have assessed autonomic functions in patients NCPF and cirrhosis.

Materials and Methods: Autonomic function such as heart rate variability (HRV) and conventional autonomic function tests (AFTs) were assessed in 3 groups of patients. Groups 1 included patients with NCPF, Group 2 were those with compensated cirrhosis (Child A) and Group 3 included age, sex and BMI-matched healthy volunteers. Patients with diabetes, cardiac or renal insufficiency, neurological disorders, on diuretics / beta blockers for at least 2 weeks prior to AFTs were excluded.

Results: Total Power (TP) of the HRV spectrum was reduced significantly in NCPF ($p<0.001$) and cirrhosis participants ($p<0.001$) when compared to the controls. LF-HF and VLF was significantly reduced in both NCPF and cirrhosis when compared to controls. LF-HF ratio was reduced in NCPF and increased in cirrhosis and the difference between them was statistically significant. There was no difference in the Mean RR of the three groups. When compared to the controls, RMSSD, SDNN, NN50 was significantly reduced in NCPF and Cirrhosis. The difference in pNN50 was significantly reduced in Cirrhosis ($p<0.001$) when compared to controls. Among Conventional AFTs, heart rate response to standing expressed as 30:15 ratio was reduced in NCPF and Cirrhosis. ΔDBP IHG was similar in all the three groups

Conclusion: The present study reports the presence of autonomic imbalance in patients suffering from NCPF and hepatic cirrhosis, which is more prominent in cirrhosis. Sympathovagal imbalance, decreased HRV, decreased vagal and increased sympathetic modulations of cardiac functions in these patients predispose them to higher CV risks and CV morbidities.

Keywords: Non-cirrhotic portal fibrosis; Cirrhosis; Autonomic function tests; Heart rate variability; Sympathovagal balance.

INTRODUCTION

Chronic liver disease is associated with various cardiovascular abnormalities, the most common characteristic of which is a hyper-dynamic circulatory state (1, 2). Autonomic dysfunction is seen in both alcoholic and nonalcoholic chronic liver diseases (3-6). Both parasympathetic and sympathetic functions are affected. The prevalence and severity of autonomic dysfunction is related to the severity of hepatic dysfunction and is independent of etiology (7). However, there are only few studies on autonomic dysfunction in Non cirrhotic portal fibrosis (NCPF) and Extra-hepatic Portal Vein Obstruction (EHPVO) in which the liver functions are normal (8, 9). The etiopathogenesis of autonomic dysfunction in NCPF is yet unexplained.

Recent studies have reported that patients with chronic liver disease have poor outcome and bad clinical presentations, if autonomic dysfunctions are present. The prevalence and severity of autonomic dysfunction appears to be related to the severity of liver disease and association of autonomic dysfunctions is linked with an increase in morbidity and mortality (5, 6). Both sympathetic and parasympathetic (vagal) functions, which can be assessed by noninvasive methods, are affected in patients with chronic liver disease (4, 5). Autonomic dysfunction in chronic liver disease may be secondary to the deranged liver function or can occur as a consequence of portal hypertension *per se* (5). Other factors such as impaired vascular hypo-responsiveness that are possibly related to a circulating vasodilator or due to presence of false neurotransmitters or a true neuropathy may also contribute. Extrahepatic portal venous obstruction (EHPVO) and non-cirrhotic portal fibrosis (NCPF) are two other diseases in which portal hypertension occurs. Previous studies have shown that a hyperkinetic circulatory state exists in patients with noncirrhotic portal hypertension, which could be

caused by expanded plasma volume secondary to enlargement of portal bed (8). To best of our knowledge the contributions of the autonomic system in modifying the systemic and portal circulation in these patients are still not known.

Recently, analysis of heart rate variability (HRV) has been reported to be a noninvasive sensitive marker in assessment of autonomic dysfunctions. Therefore, in the present study we have compared the autonomic functions in 3 groups of patients: NCPF, Child A cirrhosis and controls.

MATERIALS AND METHODS

We included all patients (>13years) who presented to Medicine and Gastroenterology units of our hospital with clinical features of NCPF and cirrhosis, over a two year and four months period (March 2011-August 2013). The research protocol was approved by our institutional ethics committee and all participants had given written informed consent.

Autonomic function was assessed in 3 groups of patients. Groups 1 included patients with NCPF, Group 2 were those with compensated cirrhosis (Child A) and Group 3 included age, sex and BMI matched healthy volunteers. Patients with diabetes, cardiac or renal insufficiency, neurological disorders, on diuretics / beta blockers for at least 2 weeks prior to Autonomic function test (AFT) were excluded.

The diagnosis of Non cirrhotic portal fibrosis in Group 1 patients was based on the presence of portal hypertension as evidenced by two out of three of the following –a) Esophageal or gastric varices on endoscopy b) USG or CT evidence of dilated portal vein (≥ 1.3 cm) c) Splenomegaly (Spleen ≥ 13 cm on USG) in the absence of liver involvement (liver biopsy s/o NCPF or no cirrhosis)

Cirrhosis (Group 2) was diagnosed based on clinical features of shrunken liver (<8cm on USG) or surface nodularity on USG, USG features (dilated portal vein >1.3cm), biochemical parameters (low albumin and prolonged prothrombin time) and/or endoscopic evidence of oesophageal/gastric varices.

Parameters assessed for AFT included Conventional AFT (30:15 Ratio, E: I Ratio, Δ DBP_{IHG} (Diastolic BP change with Isometric handgrip), Frequency Domain Analysis (FDI) and Time Domain Analysis (TDI) of HRV.

Statistical analysis of data

All categorical variables were expressed as frequencies and percentages. Chi-square test or Fisher's exact test with two tailed significance were used to compare the proportions and percentages. Continuous variables were expressed as mean, SD. The Normality of continuous variables was tested by using Kolmogorov smirnov test. One-way analysis of variance with Tukey- Krammer post-hoc test was used to compare the continuous variables between the groups. All statistical analyses were carried out for two tailed significance at 5% level of significance and p value < 0.05 were considered as significant.

RESULTS

General parameters

In the present study, the autonomic functions of 35 patients of NCPF were studied and compared with 30 controls and 30 child A cirrhosis. Out of the 35 patients of NCPF, 16 patients (45.7%) had symptoms of autonomic dysfunction in the form of dizziness on standing, postprandial epigastric bloating, early satiety, nausea or vomiting and constipation or diarrhea. The most common symptom was postprandial epigastric bloating/ early satiety in 13 patients (37%). Age, Heart rate, Mean Arterial Pressure, Systolic and diastolic blood pressure were similar in all the three groups (Table 1). BMI was significantly more in cirrhosis participants.

Frequency domain indices of HRV analysis

Total Power (TP) of the HRV spectrum was reduced significantly in NCPF ($p<0.001$) and cirrhosis participants ($p<0.001$) when compared to the controls. LF, HF and VLF was significantly reduced in both NCPF and cirrhosis when compared to controls. LF-HF ratio was reduced in NCPF and increased in cirrhosis and the difference between them was statistically significant (Table 2).

Time domain analysis of HRV analysis

There was no difference in the Mean RR of the three groups. When compared to the controls, RMSSD, SDNN, NN50 was significantly reduced in NCPF and Cirrhosis. The difference in pNN50 was significantly reduced in Cirrhosis ($p<0.001$) when compared to controls (Table 3).

Conventional AFTs

Heart rate response to standing expressed as 30:15 ratio was reduced in NCPF and Cirrhosis. ΔDBP IHG was similar in all the three groups (Table 4).

Table 1: Age, anthropometric and basal cardiovascular parameters of controls, NCPF and cirrhosis patients

Parameters	Controls (n=30)	NCPF (n=35)	Cirrhosis (n=30)	P Value
Age (years)	34.6±8.3	36.8±9.2	39.43±10.9	0.15
BMI	19.9±2.3	19.4±2.81*	21.2±2.7	0.02
Systolic BP	107.9±10.2	107.3±12.1	109.1±13.4	0.83
Diastolic BP	66.4±7.8	66.7±9.6	66.0±9.6	0.96
Heart Rate/min	71.7±9.2	71.1±12.7	72.7±13.5	0.86

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{\#}p < 0.05$

Data expressed are mean± SD. The star mark (*) depicts comparison with control and hash mark ($^{\#}$) depicts comparison between NCPF and Cirrhosis

Table 2: Frequency domain parameters of Controls, NCPF and Cirrhosis patients

Parameters	Controls (n=30)	NCPF (n= 35)	Cirrhosis (n= 30)	P value
TP (ms^2)	806.1±531.8	250.4 ±195.4***	140.57±89.7***	< 0.0001
VLF(ms^2)	182.7±149.5	55.3±46.1***	39.9±26.8***	< 0.0001
LF (ms^2)	287.4±203.3	79.4±70.1***	58.73±46.2***	< 0.0001
HF (ms^2)	335.9±289.7	115.7±100.9***	41.9±32.5***	< 0.0001
LFnu	52.8±15.9	44.4±18.0	54.9±20.8	0.053
HFnu	47.2±15.9	55.6±18.0	45.1±20.8	0.053
LF-HFratio	1.47±1.15	1.05±0.9$^{\#}$	1.7±1.1	0.04

* p < 0.05; **p < 0.01; ***p < 0.001; # p < 0.05

Data expressed are mean ± SD. The star mark (*) depicts comparison with control, hash mark (#) depicts comparison between NCPF and Cirrhosis

Table 3: Time domain parameters of controls, NCPF and cirrhosis patients

Parameters	Controls (n=30)	NCPF (n= 35)	Cirrhosis (n= 30)	P value
Mean RR(s)	83±11.66	87.97±13.92	84.67±12.61	0.2842
RMSSD(ms)	46.29±30.04	28.9±15.76**	19.88±10.89***	< 0.0001
SDNN	42.1±19.36	26.17±11.81***	22.51±15.64***	< 0.0001
NN50	68.77±65.99	37.00±44.59*	9.3±17.21***	< 0.0001
pNN50	18.57±18.51	14.37±20.12$^{\#}$	2.65±4.74***	0.0008

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{\#}p < 0.05$

Data expressed are mean ± SD. The star mark (*) depicts comparison with control and hash mark ($^{\#}$) depicts comparison between NCPF and Cirrhosis.

Table 4: Classical autonomic function testing parameters of controls, NCPF and cirrhosis patients

Parameters	Controls (n=30)	NCPF (n= 35)	Cirrhosis (n= 30)	P value
30:15 ratio	1.41±0.18	1.30±0.18*	1.25±0.16**	0.002
E: I ratio	1.33±0.2	1.27±0.13	1.21±0.12**	0.0123
Δ DBP $_{IHG}$	14.8±6.86	13.86 ±4.94	15.3±5.93	0.6072

* p < 0.05; **p < 0.01

Data expressed are mean ± SD. The star mark (*) depicts comparison with control

DISCUSSION

The total power (TP) of heart rate variability (HRV) was significantly less in both NCPF and cirrhosis groups suggesting that in NCPF and cirrhosis patients the vagal modulation of cardiac functions is considerably reduced as TP of HRV in general represents the magnitude of cardiac parasympathetic activity (10, 11). TP represents the enormity of heart rate variability, which is primarily a vagal function, and decreased TP is the index of decreased HRV (10, 11). It has been reported that decreased HRV is associated with increased cardiovascular (CV) risks, and all cause morbidity and mortality (12-14). Thus, decreased TP in NCPF and cirrhosis groups indicates increased CV risks in these patients. Among NCPF and cirrhosis groups, the TP in cirrhosis group was about 45% less compared to NCPF group, suggesting that the cirrhosis patients are more vulnerable to CV risks, morbidities and mortality. Further, HFnu and time-domain indices (RMSSD, SDNN, NN50, and pNN50) of HRV were significantly less in cirrhosis patients compared to NCPF patients. These findings establish the greater decrease in vagal potency in cirrhotic patients compared to NCPF patients, as HFnu and time-domain indices are measures of parasympathetic drive of cardiac control (10, 11). Suggesting that cirrhotic patients more susceptible to CV morbidities.

In addition, The LF-HF ratio was more in cirrhosis group compared to NCPF group, indicating a greater sympathovagal imbalance in cirrhotic patients, as LF-HF ratio is a marker of sympathovagal imbalance and increased sympathetic activity (10, 11). This was further evidenced by increased LFnu in cirrhosis group compared to NCPF group, as LFnu is a marker of sympathetic drive to the heart (10, 11). Thus, these findings indicate that cirrhotic patients had increased sympathetic activity compared to NCPF patients. Findings of the present study also indicate that sympathovagal imbalance is more in hepatic cirrhosis compared to NCPF, which is due to both decreased vagal activity and increased sympathetic activity.

On analysis of conventional autonomic function tests (CAFT), it was found that 30:15 ratio and E: I ratio were decreased in NCPF and cirrhosis group

compared to control group, and the decrease was more pronounced in cirrhosis group. As, both 30:15 ratio and E:I ratio are measures of parasympathetic reactivity (15), these findings indicate decreased vagal reactivity in NCPF and cirrhosis, which is more in cirrhotic patients compared to NCPF patients. However, there was no significant alteration in sympathetic reactivity in these patients, as there was no significant difference in ΔDBPIHG, the marker of sympathetic reactivity (15), among the groups.

Findings of the present study indicate the presence of sympathovagal imbalance in NCPF and cirrhosis group, which is more intense in cirrhotic patients. The sympathovagal imbalance is contributed by both decreased parasympathetic activity and increased sympathetic activity. Though there is decreased parasympathetic reactivity, sympathetic activity remains unaltered. Thus, these findings indicate that the autonomic imbalance in NCPF and hepatic cirrhosis patients are mostly due to the reduction in vagal component of autonomic modulation, though increased sympathetic activity contribute to some extent. Though the exact cause of greater degree of sympathovagal imbalance in cirrhotic patients cannot be ascertained from this study, increased body mass index (BMI) might be a potential contributor to the autonomic imbalance, which was significantly high in cirrhosis group compared to NCPF group, as increase in BMI has been reported to decrease parasympathetic and increase sympathetic activity.[15] However, the cause-effect relationship between BMI and autonomic imbalance cannot be established from the findings of the present study.

The present study reports the presence of autonomic imbalance in patients suffering from NCPF and hepatic cirrhosis, which is more prominent in cirrhosis. Sympathovagal imbalance, decreased HRV, decreased vagal and increased sympathetic modulations of cardiac functions in these patients predispose them to higher CV risks and CV morbidities. An earlier study reported autonomic dysfunction in 12 (67%) patients with EHPVO, 3 (25%) patients with NCPF and 12 (80%) patients with cirrhosis (7). However, only 3 patients had NCPF in their study population and frequency domain parameters were not studied. Another study has shown greater likelihood of variceal bleed in NCPF cases with autonomic dysfunction (8). Autonomic dysfunction was reported in patients with extra-hepatic portal vein thrombosis, however there was no correlation with hemodynamic abnormalities (9).

Non-cirrhotic portal fibrosis (NCPF) is one of the important causes of upper gastrointestinal hemorrhage in a patient with normal liver function in tropical countries. It causes presinusoidal portal hypertension and hypersplenism (16, 17). NCPF patients with dysautonomia are prone to frequent falls, gastrointestinal symptoms which hamper their quality of life. In this study, dysautonomia was found in all 24 NCPF patients, of whom10 were symptomatic. Portal hypertension is the underlying pathology in both cirrhotic and non cirrhotics. In cirrhosis, endocannabinoids and excess nitric oxide production has been implicated as a causative factor (18, 19). The exact etiology is not known in NCPF. Prognosis is worse in cirrhotics with autonomic dysfunction (20, 21). In earlier studies, cirrhosis patients were found to have objective evidence of improvement in cardiovascular parameters post-transplant (22, 23). Future research can elucidate the role of endotoxins in causation of dysautonomia in patients of NCPF and correlate its prognostic significance.

Study limitations are that it's a cross sectional study. More longitudinal studies are needed to establish causality between NCPF and dysautonomia. Also, we did not study the quality of life indicators in these patients. Cirrhosis patients were diagnosed based on ultrasonography and laboratory parameters and biopsy was not undertaken. We have not estimated the biochemical markers of CV risks in these patients and the sample size is less in each group. Due to less sample size, the multiple regression analysis could not be done to assess the link of BMI to sympathovagal imbalance in these patients. Future studies on larger sample size are warranted to assess if CV risks in NCPF and hepatic cirrhosis are linked to autonomic imbalance, and the interventions required to reduce the CV risks in patients suffering from these disorders.

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