

## **Assessment of Autonomic Nervous Activity in Chronic Liver Disease**

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### **Abstract**

**Study of autonomic nervous system activity in chronic liver disease has aroused great interests due to its increasing prevalence due to various etiologies. The present study was undertaken to assess the autonomic nervous system activity in chronic liver disease patients by five standard autonomic function tests. Forty patients (20 with alcoholic liver disease and 20 with non- alcoholic liver disease) and 40 normal healthy age sex matched controls were recruited in the study. Statistical analysis comprised student's "t" test. Thirty out of the 40 patients (75%) were found to have autonomic dysfunction. Fourteen out of 30 patients (46.67%) had only parasympathetic damage and 16 out of 30 (53.53%) had combined sympathetic and parasympathetic damage. Eighty percent of the alcoholic liver disease patients and 70 % of the non- alcoholic liver disease patients showed autonomic dysfunction. In conclusion, autonomic nervous dysfunction is present in significant number of patients with chronic liver disease. Overall; the parasympathetic impairment was more frequently present in chronic liver disease patients than sympathetic impairment . Autonomic dysfunction is found with comparable frequency in alcoholics and non-alcoholics suggesting that chronic liver disease, irrespective of etiology, contributes to autonomic dysfunction. The clinical implication of our study is that keeping in view the significant prevalence of autonomic dysfunction caution should be exercised while managing chronic liver disease patients as cirrhotic cardiomyopathy can be unmasked by surgical intervention.**

**Key words:** Autonomic dysfunction, chronic liver disease, autonomic function tests

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### **Introduction**

Autonomic nervous system (ANS) activity is influenced by various physiological and pathological conditions. Autonomic neuropathy is well described in Diabetes mellitus, cerebrovascular disease, spinal cord lesions, Shy Drager syndrome and with use of certain drugs [1]. Currently, study of ANS activity in chronic liver disease (CLD) has aroused great interests due to reports on role of autonomic dysfunction in prognosis of CLD patients and increasing prevalence of CLD due to various etiologies.

The most common causes of chronic liver disease in general order of frequency are chronic hepatitis C, alcoholic liver disease (ALD), non-alcoholic steatohepatitis, chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease [2]. In India, the prevalence of CLD is increasing due to various etiologies. 2% of the total Indian population is HCV carrier. There are an estimated 43-45 million HBsAg carriers and, among them 10-12 million also have HBeAg [3,4]. Prevalence of ALD is also in-

creasing due to increasing trend of alcohol consumption [5,6].

CLD is accompanied by a number of circulatory changes including impairment of cardiovascular autonomic reflexes, related in part to an autonomic neuropathy. As in diabetes, autonomic dysfunction in CLD results in inadequate response to stressful events like sepsis and hemorrhage [7],[8]. So the possible role of autonomic nervous activity status in management of CLD patients is being recognized nowadays.

In India very few studies regarding autonomic dysfunction in CLD have been conducted. Therefore this study was planned primarily to assess the extent of autonomic dysfunction in CLD and to study the relation between underlying etiology of CLD and the autonomic dysfunction, if any.

### **Materials and Methods**

The study was conducted on 40 patients with chronic liver disease (20 alcoholic liver disease and 20 non- alcoholic

liver disease) and 40 age-sex matched controls in the Department of Physiology, Government Medical College and Guru Nanak Dev Hospital Amritsar, India.

The diagnosed cases of CLD, based on, clinical examination, raised liver function tests for >6 months [2] and ultrasound findings were recruited in the study. All patients belonged to Child's Grade B [9]. Subjects with a history of diabetes mellitus, heart disease or who were on medication likely to influence the interpretation of the autonomic tests such as diuretics or beta-blockers were excluded from the study. Forty normal, healthy, age sex matched controls were recruited from the local population. Both cases and controls gave informed consent and clearance from institutional ethics committee was obtained. A detailed history was taken from these subjects and a thorough physical examination including general physical and neurological, was carried out. All the subjects were subjected to the five standard autonomic function tests. Heart rate response to valsalva manoeuvre, heart rate ( R-R interval ) variation during deep breathing and immediate heart rate response to standing tests the parasympathetic system while blood pressure response to sustained hand grip and blood pressure response to standing tests the sympathetic system.

#### ***Heart rate response to Valsalva manoeuvre.***

The test was performed by the subject, blowing into the mouth piece attached to a manometer and holding it to a pressure of 40 mmHg for 15 seconds while a continuous electrocardiogram was recorded. The manoeuvre was performed 3 times at one minute intervals. The result was expressed as: Valsalva ratio= Longest R-R interval after the manoeuvre / Shortest R-R interval during the manoeuvre The mean of the three valsalva ratios was taken as the final result.

#### ***Heart rate ( R-R interval ) variation during deep breathing. (Deep breathing test)***

The subject was asked to breath deeply at 6 breaths/min (5 seconds 'in' and 5 seconds 'out') for one minute. ECG was recorded throughout the period of deep breathing and onset of each inspiration and expiration was marked on ECG paper. The maximum and minimum R-R intervals during each breathing cycle were measured with a ruler and converted to beats/min. The results of the test were expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats/min.

#### ***Blood Pressure response to sustained hand grip.***

In this test the blood pressure of the subject was taken three times before the manoeuvre. The maximum voluntary contraction was first determined using a handgrip dynamometer. Handgrip was then maintained at 30% of their maximum for as long as possible upto 5 min. BP was measured at 1 min intervals during the handgrip. The

result was expressed as the difference between the highest diastolic blood pressure during handgrip exercise and the mean of the three diastolic blood pressure readings before the test.

#### ***Immediate heart rate response to standing ( 30:15 Ratio)***

The test was performed with the subject lying quietly on a bed while heart rate was being recorded continuously on an electrocardiogram (BPL Cardiart 108T/MK-VI ) The subject was then asked to stand unaided and the point at starting to stand was marked on ECG paper. The shortest R-R interval at or around 15th beat and the longest R-R interval at or around 30<sup>th</sup> beat after starting to stand were measured with a ruler. The characteristic HR response was expressed as 30:15 ratio.

#### ***Blood pressure response to standing***

In this test the subject's blood pressure was measured with a sphygmomanometer while he was lying quietly and one minute after he was made to stand up. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and systolic pressure standing. The test was repeated three times and the mean was calculated.

The subjects were briefed about these five standard autonomic function tests. Self demonstration of the tests was done to make them conversant with the procedure and to remove apprehension regarding the tests, if any.

Interpretation of tests was based on guidelines of Ewing and Clarke [10]. (Table 1). Subject was labeled 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 parasympathetic tests were abnormal; and with combined parasympathetic and sympathetic damage, if in addition to parasympathetic damage, at least one of the two sympathetic function tests was abnormal. The borderline tests were interpreted as normal [11]. The results of the five standard autonomic tests in patients and controls were compared using the student's t-test.

## **Results and Discussion**

Autonomic dysfunction is an extrahepatic manifestation of CLD. Only a few Indian studies regarding this subject have been published [12,13]. In our study, the comparison of mean values of standard autonomic function tests in controls and patients (Table 2 and Table 3) shows that highly significant change in autonomic nervous system activity is seen in CLD patients. Amongst the parasympathetic function tests the difference between CLD patients and controls for the 30:15 ratio and deep breathing test was highly significant (p value < 0.001). Amongst the sympathetic function tests the difference between CLD patients and controls for the diastolic BP rise during hand

grip test was highly significant (p value < 0.001). 30:15 ratio was the most frequently abnormal test in our study.

The distribution of autonomic dysfunction in various groups of CLD (Table 4) shows that overall in our study, 30 out of the 40 CLD patients (75%) were found to have autonomic dysfunction. Fourteen out of 30 CLD patients (46.67%) had only parasympathetic damage and 16 out of 30 (53.33%) had combined sympathetic and parasympathetic damage. None of the subjects had sympathetic dysfunction alone. Overall parasympathetic impairment was more than sympathetic impairment in CLD patients.

Gentile et al found autonomic neuropathy in 60 % of the 113 cirrhotic. Seventy one percent of alcoholics and 57 % of non- alcoholics were affected. The parasympathetic impairment was significantly more than sympathetic impairment [14]. Dillon et al also detected abnormal cardiovascular autonomic reflexes in 60% of the 70 CLD patients [15]. Study by Bajaj et al on 20 CLD patients of Indian origin showed that 16 out of 20 (80%) of the CLD patients had evidence of autonomic dysfunction. Of these, 8 (40%) had combined parasympathetic and sympathetic

damage and 8 (40%) had parasympathetic damage only [12]. Our results are in accordance with these studies.

In our study autonomic dysfunction is found with comparable frequency in alcoholics (80%) and non-alcoholics (70%) suggesting that liver damage, irrespective of etiology, can contribute to autonomic dysfunction. Similar findings were drawn by MacGilchrist and Reid in their study on 20 cirrhotics [16].

The present study differs from that of Barter and Tanner [10]. In their study on 30 CLD subjects parasympathetic damage was reported in 16% and combined parasympathetic and sympathetic damage in additional 20%. The lower frequency of autonomic dysfunction in their study could be due to the fact that they included only 14 subjects with alcoholic liver disease while the rest had an alcohol dependence problem only. Our study differs from that of Hendrickse et al also [17]. They reported vagal neuropathy in 45% of the 60 CLD patients. The lower frequency of autonomic neuropathy reported is due to the fact that 57 out of 60 CLD patients belonged to Child class A. In our study all patients belonged to Child class B.

**Table 1.** Interpretation of Autonomic function tests

Test	Autonomic function tested	Normal	Borderline	Abnormal
Heart rate response to standing (30:15 Ratio)	Parasympathetic	≥ 1.04	1.01-1.03	≤ 1.00
Deep breathing Test (max-min heart rate in beats/min)	Parasympathetic	≥ 15	11-14	≤ 10
Valsalva Ratio	Parasympathetic	≥ 1.21	1.11-1.20	≤ 1.10
Blood Pressure response to standing (fall in Systolic BP in mm Hg)	Sympathetic	≤ 10	11-29	≥ 30
Blood Pressure response to sustained hand grip (increase in diastolic BP in mm Hg)	Sympathetic	≥ 16	11-15	≤ 10

**Table 2** Comparison of parasympathetic function tests

Parameter	CLD Patients (Mean ± SD)	Controls (Mean ± SD)	P value
30:15 Ratio	0.97 ± 0.08	1.04 ± 0.03	< 0.001; HS
Valsalva Ratio	1.20 ± 0.25	1.32 ± 0.20	< 0.05; S
Deep Breathing test (DBT)	14.53 ± 8.63	20.95 ± 8.07	< 0.001; HS

*SD – Standard Deviation*

*S: Significant; HS: Highly Significant*

**Table 3.** Comparison of sympathetic function tests.

Parameter	CLD Patients (Mean ± SD)	Controls (Mean ± SD)	P value
HGT (Rise in DBP)	13.25 ± 6.89	20.45 ± 3.55	< 0.001; HS
BP response on standing. (Fall in SBP)	11.00 ± 5.69	10.30 ± 4.59	> 0.05; NS

SD – Standard Deviation

NS: Not Significant; HS: Highly Significant

**Table 4.** Distribution of autonomic dysfunction in CLD patients.

Patient Group	Autonomic Dysfunction Cases	Type of Autonomic Damage	
		Only Parasympathetic	Parasympathetic and Sympathetic
Total CLD patients (n = 40)	30 (75.00%)	14 (46.67%)	16 (53.33%)
ALD Patients (n=20)	16 (80%)	06 (37.5%)	10 (62.5%)
Non-ALD Patients (n=20)	14 (70%)	08 (57.1%)	06 (42.86%)

The findings of our study have clinical implications. The systemic circulation in patients with CLD is hyperdynamic with an increased cardiac output and heart rate and a reduced systemic vascular resistance caused by humoral and nervous dysregulation.[18,19]. It is suggested that autonomic neuropathy plays a role in development of this hyperdynamic circulation in CLD [20,21]. Nowadays there is easy availability of the transjugular intrahepatic portal systemic shunt (TIPS), peritoneal venous shunting, liver transplantation to the large number of CLD patients, even in the developing countries like India. Keeping in view the significant prevalence of autonomic dysfunction, as suggested in our study, caution should be exercised during these stressful procedures as the cirrhotic cardiomyopathy, an entity different from the heart muscle disease, can be unmasked by physical or pharmacological strain [22]. Autonomic function status may be evaluated before going in for the above said procedures.

Finally, considering the possibility of adverse prognostic implications of the autonomic neuropathy in CLD and clinical significance of cirrhotic cardiomyopathy, caution may be exercised while managing CLD patients.

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