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A STUDY OF CARDIOVASCULAR AUTONOMIC FUNCTION IN ALCOHOLIC-FATTY LIVER DISEASE AND NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS

Physiology

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ABSTRACT

Background: Cardiovascular autonomic dysfunction is found in fatty liver disease irrespective of its etiology. **Aims and Objectives:** The aim of the present study was to compare the cardiovascular autonomic function between patients with alcoholic-fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). **Materials and Methods:** The study was conducted on 102 patients with fatty liver disease (46 AFLD and 56 NAFLD). Autonomic function test was done in the Department of Physiology, JNIMS by utilizing "Ewing's battery of tests". Statistical analysis was done by applying independent t test. **Results:** The mean difference for SHGT was statistically significant between the patients with AFLD and NAFLD while the mean differences for the remaining variables like Valsalva ratio (VR), HR variation during deep breathing (δHR), HR response to standing (30:15 ratio) and BP response to standing were not statistically significant. The most common autonomic dysfunction found in patients with AFLD was combined sympathetic and parasympathetic dysfunction (37%) while in patients with NAFLD, it was early parasympathetic dysfunction (33.9%). **Conclusion:** Autonomic dysfunction is found in comparable frequency between patients with AFLD and NAFLD. Since, fatty liver disease with autonomic dysfunction is associated with poor prognosis, due importance should be given to assessment of autonomic function in patients with fatty liver disease.

KEYWORDS

Cardiovascular autonomic function, fatty liver disease

INTRODUCTION

The liver is one of the most important organs of our body and has various functions such as detoxification, synthesis of protein, production of biochemicals, glycogen storage, decomposition of red blood cells and production of hormone. The major causes of chronic liver diseases are viral hepatitis, autoimmune hepatitis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cirrhosis and hepatocellular carcinoma.[1]

Globally, it is reported that 844 million people have chronic liver disease with a mortality rate of 2 million deaths per year.[2] The estimated prevalence of alcoholic liver disease is 8.5% while that of non-alcoholic fatty liver disease (NAFLD) is 25% in the world.[3,4] In India, a study reported that the prevalence of alcoholic liver disease comprises of only 25%.[5] Another Indian epidemiological study reported that the prevalence of NAFLD is around 9% to 32% of general population with higher prevalence found in those with Obesity and Diabetes.[6]

Chronic liver disease is accompanied with various changes in electrolyte balance, altered regulation and response to vasoconstrictors and vasodilators, changes to the arterio-venous circulation and other immunological and physiological changes which give an effect on autonomic function.[7] Cardiovascular autonomic neuropathy is the most serious complication of chronic liver disease.[8] Hendrickse et al.[9] observed that cardiovascular autonomic dysfunction is more common in advanced liver disease patients than those with early liver disease patients. Coelho et al.[10] also demonstrated that the more severe the hepatopathy, the greater is the impairment.

There are few documented information on comparison of cardiovascular autonomic function between alcoholic and non-alcoholic fatty liver disease patients from India. Therefore, the present study was done to compare the cardiovascular autonomic functions between patients with alcoholic fatty liver disease and non-alcoholic fatty liver disease.

MATERIALS AND METHODS

The study was conducted on 102 patients with fatty liver disease (46 alcoholic fatty liver disease and 56 non-alcoholic fatty liver disease) with age ranged from 23-60 years in the Department of Physiology, Jawaharlal Nehru Institute of Medical Sciences, JNIMS. All the patients were recruited from Out-patient Department of Medicine, JNIMS. Out of 102 patients, 58 patients were males and 44 patients were females. Alcoholic fatty liver disease patients comprises of males only as alcoholic females do not attend OPD due to social stigma/ culture. Inclusive criteria for AFLD were patients who had a significant history of alcohol consumption exceeding 210 gm/week in males and 140gm/week in females for the last 2 years and ultrasound showing fatty liver whereas patients with no history of alcohol consumption and ultrasound showing fatty liver were taken for NAFLD. Patients with history of hepatitis, diabetes mellitus, thyroid disorders, heart disease or who were using drugs which can affect the autonomic function tests (e.g. phenytoin, amiodarone, propanolol, methyldopa etc) were excluded from the study.

The study was carried out after taking clearance from the Institutional Ethics Committee (IEC number : 112(5)) of JNIMS. Prior to participation for the study, the purpose of the study was explained to all the subjects and informed written consent was taken.

All the subjects were asked to come to Autonomic Laboratory, Department of Physiology, JNIMS. Autonomic function test was done by utilizing "Ewing's battery of tests".

Cardiovascular parasympathetic status assessment was done by:

i) Deep breathing test

The patient was instructed to maintain deep breathing at a rate of six breaths per minute and was made to lie down comfortably in supine position with head elevated to 30 degrees. Electrocardiogram (ECG) electrodes was connected for recording ECG (lead II) using the single channel Student's Physiograph, INCO While patient was breathing deeply at the rate of 6 breaths per minute (allowing 5 seconds each for inspiration and expiration), maximum and minimum heart rates was recorded with each respiratory cycle. Expiration to inspiration ratio (E:I ratio) was determined as the sum of 6 longest R-R intervals, each of 6 repetitions divided by the sum of 6 shortest R-R intervals. The maximum and minimum R-R was identified and converted into HR, giving the HRV in one minute (δ HR).

ii) Heart rate response to standing

The patient was made to lie down in supine position. The patient was asked to relax completely for a minimum period of 10 minutes. The resting ECG was recorded, and basal heart rate was determined. The patient was asked to stand up immediately and remain motionless while ECG was recorded for 1-3 minutes. Heart rate response to standing was determined by using the 30:15 R-R ratio which was longest RR interval occurring about 30 beats after standing divided by shortest RR interval which occurred about 15 beats after standing.

iii) Heart rate response to Valsalva manoeuvre

The patient was made to sit in a comfortable position. Nose was clipped with the help of a nose-clip. The mouth-piece was put into the mouth of the patient and the mercury manometer was connected to the mouthpiece. ECG (Lead II) was recorded continuously. The patient was asked to exhale forcefully into the mercury manometer and was asked to maintain the expiratory pressure at 40 mm Hg for 10-15 seconds. ECG was recorded throughout the procedure, 30 seconds before and after the procedure. Valsalva ratio (VR) was calculated from the relation of longest R-R interval obtained during the continuous ECG monitoring after strain to the shortest R-R interval during strain.

Cardiovascular sympathetic status assessment was done by:

i) Sustained hand grip test (SHGT):

After recording the basal blood pressure, the patient was asked to grip a hand dynamometer three times with his/her dominant hand using maximal effort, at an interval of two minutes each. All the three readings on the dynamometer (force generated by subject in kg) were noted and 30% of mean maximal voluntary capacity was calculated. The patient was then asked to grip the dynamometer at 30% of his/her maximum capacity and to maintain it for 2-3 minutes. Blood pressure (BP) was recorded in the contra-lateral arm every minute during contraction. Maximum change in both systolic and diastolic BP was compared with basal BP.

ii) Blood pressure response to standing

After making patient to lie down supine for 5 minutes, basal BP recording was done. The patient was then asked to stand up and BP was recorded at 0 and 1 minute intervals. Change in BP was given by difference between the basal BP and BP during standing.

Interpretation of tests

Interpretation of tests was based on the guidelines of Ewing and Clarke.[11] 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 one or both the tests of the sympathetic function were abnormal in addition to parasympathetic damage. For the purpose of the above mentioned classification the borderline tests were interpreted as normal.[12]

In our study, we have taken those patients who were having definite parasympathetic dysfunction and combined sympathetic and parasympathetic dysfunction for estimation of autonomic dysfunction.

Statistical analysis

The data were entered in MS Excel and Statistical Package for Social Sciences (SPSS) version 23 was used for statistical analysis. All the values were expressed as mean ± S.D and percentage. Analytical statistics was done by applying independent t test. 'p' value of less than 0.05 was considered significant.

RESULTS

Table 1 shows the interpretation of autonomic function tests.

Table 2 shows the demographic profile of patients with AFLD and NAFLD. The mean differences for age (p value < 0.05) and height (p value < 0.001) were found to be statistically significant while the mean differences for weight and BMI were insignificant.

Table 3 shows a significant difference in the basal SBP (p value <0.05) and basal HR (p value < 0.001) while there is no significant difference in the basal DBP when compared between patients with AFLD and NAFLD.

Table 4 shows the comparison of cardiovascular autonomic function tests between patients with AFLD and NAFLD. The mean difference for SHGT was statistically significant (p value < 0.05) between the patients with AFLD and NAFLD while the mean differences for the remaining variables like Valsalva ratio (VR), HR variation during deep breathing (δHR), HR response to standing (30:15 ratio) and BP response to standing were not statistically significant (p-value>0.05).

Table 5 shows the proportion of patients with AFLD and NAFLD showing early parasympathetic dysfunction, definite parasympathetic dysfunction, combined sympathetic and parasympathetic dysfunction and normal autonomic function. The most common autonomic dysfunction found in patients with AFLD was combined sympathetic and parasympathetic dysfunction (37%) while in patients with NAFLD, it was early parasympathetic dysfunction (33.9%).

Table 1. Interpretation of autonomic function tests

Tests	Method	Normal	Borderline	Abnormal
Heart rate response to Valsalva manoeuvre	Valsalva ratio	≥1.21	1.11-1.20	≤1.10
Heart rate variation during deep breathing (by ECG)	Maximum-minimum of heart rate	≥15 beats/min	11-14 beats/min	≤10 beats/min
Immediate heart rate response to standing (by ECG)	R-R interval ratio of 30th beat:15th beat	≥1.04	1.01-1.03	≤1.00
Blood pressure response to standing	Measure blood pressure in supine and then in stand	≤10 mmHg	11-29 mmHg	≥30 mmHg
Blood pressure response to sustained handgrip (2 min)	Measure diastolic blood pressure after 2 min using of hand grip	≥16 mmHg	11-15 mmHg	≤10 mmHg

Table 2: Demographic profile of patients with AFLD and NAFLD

Characteristics	AFLD (n=46) (Mean ± SD)	NAFLD (n=56) (Mean ± SD)	p-value
Age (years)	46.98 ± 9.33	43.24 ± 9.0	0.045
Weight (Kg)	63.00 ± 9.37	63.15 ± 11.71	0.946
Height (cm)	159.33 ± 5.29	149.78 ± 7.22	0.000
BMI (Kg/m2)	24.17 ± 4.06	25.60 ± 5.81	0.164

"p <0.05" was taken as significant, n: number of patients, BMI: Body Mass Index

Table 3: The mean ± SD values of basal BP and basal HR between patients with AFLD and NAFLD

Characteristics	AFLD (n=46) (Mean ± SD)	NAFLD (n=56) (Mean ± SD)	p-value
Basal SBP (mmHg)	134.82 ± 17.57	127.24 ± 18.97	0.042
Basal DBP (mmHg)	85.32 ± 10.13	84.58 ± 8.49	0.692
Basal HR (bpm)	85.71 ± 14.9	73.36 ± 14.0	0.000

"p <0.05" was taken as significant, n: number of patients, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, bpm: beats per minute

Table 4: Comparison of cardiovascular autonomic function tests between patients with AFLD and NAFLD

AFT variables	AFLD (n=46) (Mean ± SD)	NAFLD (n=56) (Mean ± SD)	p-value
Valsalva ratio (VR)	1.20 ± 0.09	1.19 ± 0.09	0.860
HR variation during deep breathing, δHR (bpm)	14.44 ± 8.45	11.85 ± 5.13	0.062
HR response to standing (30:15 ratio)	1.08 ± 0.062	1.06 ± 0.093	0.214
BP response to standing (mmHg)	12.36 ± 14.60	8.20 ± 8.75	0.082
BP response to sustained hand grip (mmHg)	16.22 ± 5.97	14.11 ± 4.22	0.041

"$p < 0.05$ " was taken as significant, n: number of patients, HR: Heart rate, bpm: beats per minute, BP: blood pressure

Table 5. Proportion of autonomic function status among the patients with AFLD and NAFLD

Status of autonomic function	AFLD (n=46) n (%)	NAFLD (n=56) n (%)	Total (n=102) n (%)
Early parasympathetic dysfunction	9 (19.6)	19 (33.9)	28 (27.5)
Definite parasympathetic dysfunction	8 (17.4)	18 (32.1)	26 (25.5)
Combined sympathetic and parasympathetic dysfunction	17 (37.0)	10 (17.9)	27 (26.5)
Normal	12 (26.1)	9 (16.1)	21 (20.6)
Total	46 (100)	56 (100)	102 (100)

n: number of patients, %: percentage

DISCUSSION

In the present study, the values of basal systolic blood pressure (p value < 0.05) and basal heart rate (p value < 0.001) were significantly higher in patients with AFLD as compared to patients with NAFLD. These may be due to alteration of autonomic function. Earlier study by Houghton et al.[13] also found that basal mean blood pressure was 5% higher in dual (hepatic steatosis and alcohol) aetiology fatty liver disease (DAFLD) group than in NAFLD group. Moreover, they also reported that the parasympathetic activity was 29% lower (nu-DBP) in DAFLD groups than those with NAFLD.

In our study, we found that Valsalva ratio was the most common abnormal test followed by heart rate variation during deep breathing while BP response to standing was the least abnormal test in both groups of patients. We also observed that the mean value of BP response during SHGT was significantly different when compared between patients with AFLD and NAFLD (p value <0.05). Gentile et al.[14] reported that deep breathing test and handgrip test were mostly influenced by the compliance of the patient. In their study, they also found that the deep breathing test was the most altered test while lying to standing test was the most sensitive and specific test. In our study, there were no statistically significant differences of heart rate variation during deep breathing, heart rate response to standing, Valsalva ratio and BP response to standing when compared between patients with AFLD and NAFLD.

A study by Oliver et al.[15] reported that 63% of patients with non-alcoholic chronic liver disease had shown abnormal peripheral sympathetic test. Among the vagal tests, Valsalva ratio was abnormal in 46% and abnormal heart rate variability in response to deep breathing was seen in 36% which is similar with our findings.

In contrast with our findings, study by Deka et al.[16] on 60 patients with alcoholic liver disease observed that the heart rate response to standing was the most common abnormal test. Another study by Milovanovic et al.[17] reported that 16 out of 25 patients with alcoholic cirrhosis admitted in the hospital had at least one or more abnormal parasympathetic function test. They also reported that heart rate response to standing was the most common abnormal test which could be due to blunted baroreflex function. Impaired baroreflex function seen in liver disease could be related to activated renin- angiotensin-aldosterone system as the cardiac response to standing normalizes on administration of canrenone.[18]

The present study found that combined sympathetic and parasympathetic dysfunction was the most common dysfunction seen among the patients with AFLD whereas early parasympathetic dysfunction was the most common among the patients with NAFLD. We also found that 54.4% of patients with AFLD and 50% of patients with NAFLD had autonomic dysfunction.

Singh et al.[19] assessed autonomic nervous activity in 40 chronic liver disease patients (20 with alcoholic liver disease and 20 with non-alcoholic liver disease) by using five standard autonomic function tests and found that 80% of alcoholic liver disease patients and 70% of non-alcoholic liver disease patients had autonomic dysfunction. They also observed that the parasympathetic impairment was more frequently present than combined sympathetic and parasympathetic impairment. Study by Hendrickse et al.[20] also observed that autonomic dysfunction was equally seen in patients with alcohol-related (47%) and non-alcohol related (44%) liver disease. Thuluvath and Triger [21] also reported that 45% of patients with alcoholic liver disease and 43% with non-alcoholic liver diseases showed parasympathetic neuropathy. They also observed 11% patients with alcoholic liver disease and 12% with non-alcoholic liver disease had sympathetic dysfunction. Their study indicated that autonomic dysfunction was present in comparable frequency between the patients with alcoholic and non-alcoholic fatty liver disease suggesting that neurological defect may be the result of disturbed liver function.

The association between fatty liver disease and autonomic dysfunction is not clearly understood. However, previous study has reported that there is an association between liver fat and insulin resistance.[22] A study by Houghton et al.[13] showed that insulin resistance was significantly related with reduced heart rate variability suggesting altered autonomic function. Insulin clearance by the liver is decreased with elevated levels of free fatty acids. There may be a role of hepatoportal vagal sensing of lipids in the pathophysiology of hepatic insulin resistance.[23]In addition, a study by Ziegler et al.[24] reported that increased hepatic fat content was strongly associated with both lower cardiovagal tone and baroreceptor sensitivity (BRS).They also found that vagus modulated HRV indices and BRS have an inverse relation with liver fat content. Therefore, it could be deduced from the above studies that hepatic fat and insulin resistance may contribute to autonomic disturbances in fatty liver disease patients.

CONCLUSION

We can conclude from our study that autonomic dysfunction is present in comparable frequency between patients with AFLD and NAFLD. Valsalva ratio is the most common abnormal test seen in both groups of patients (AFLD and NAFLD). Since, fatty liver disease with autonomic dysfunction is associated with poor prognosis, due importance should be given to assessment of autonomic function in patients with fatty liver disease.

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Conflict of interest

There are no conflicts of interest about the research article.

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