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RESEARCH ARTICLE

Dysautonomia in heavy drinkers for more than 5 years of alcoholic consumption with intact liver function

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ABSTRACT

Background: It is known for long that alcoholic liver cirrhosis is characterized by autonomic dysfunction due to the underlying liver pathology. However, alcohol can have a direct effect on the autonomic functions even before the liver functions are altered. **Aims and Objectives:** We have undertaken this study to test and compare the autonomic function status in apparently healthy alcoholics with normal liver function tests with age- and sex-matched healthy individuals. **Materials and Methods:** Thirty healthy non-alcoholics with normal liver function as controls and 30 apparently healthy alcoholics for more than 5 years with normal liver function tests were taken for this study. Autonomic function tests for both parasympathetic and sympathetic functions were performed in both these groups, and the results were compared. **Result:** Parasympathetic function tests were within the normal range except for the resting heart rate (HR) which showed a significant increase ($P < 0.01$) in the study subjects compared with the controls. Sympathetic tests showed a very significant increase in blood pressure (BP) response to postural change and a significant change in handgrip test. **Conclusion:** Resting HR and BP response to postural change were increased and BP response to handgrip test has shown a significant change in study subjects compared to controls which suggest that both sympathetic and parasympathetic functions are altered in them. We will conclude this study with the findings that alcohol has a direct effect on the autonomic nervous system even without any liver function tests alteration.

KEY WORDS: Chronic Alcoholism; Intact Liver Function Tests; Autonomic Nervous System; Parasympathetic Dysfunction; Sympathetic Over Activity

INTRODUCTION

The autonomic nervous system, a division of the peripheral nervous system, influences the function of internal organs. It comprises the sympathetic and parasympathetic nervous system. They are largely responsible for the involuntary, subconscious control of viscera, smooth muscle, and secretory glands.[1]

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Autonomic dysfunction/dysautonomia is the neuropathy affecting the autonomic nervous system. It may be due to inherited or degenerative neurologic diseases (primary dysautonomia) or it may be due to injury of the autonomic nervous system from an acquired disorder (secondary dysautonomia), and the symptoms often develop gradually over years.[2]

The pathophysiological basis of autonomic dysfunction secondary to liver disease is largely unknown. Immunological and metabolic abnormalities may play a role, but the resultant decreased parasympathetic and increased sympathetic activity may in part is explained by the following mechanisms.[3] There is a decreased response to vasoconstrictors which may be caused by increased concentration of vasodilators such as nitric

oxide. An increase in portal blood pressure (BP), even mild, can lead to an upregulation of nitric oxide synthetase. An increase in circulating vasodilators, a diseased liver, and a portosystemic circulation bypassing hepatic metabolism will contribute to increased levels of vasodilators. Circulating vasodilators will activate the renin-angiotensin-aldosterone system and increase plasma levels of the vasoconstrictor-angiotensin II. Plasma concentrations of angiotensin II are raised in patients with chronic liver disease and correlate with disease severity.[3] Autonomic dysfunction in advanced liver disease is associated with decreased baroreceptor sensitivity to hypotension, leading to impaired BP and heart rate (HR) responses.[3]

Many studies have been undertaken on the effect of alcoholism on autonomic function tests and concluded that the underlying liver pathology due to chronic alcoholism led to the autonomic dysfunction in them.

Thus, the present study is undertaken to test and establish the autonomic functions in apparently healthy subjects with more than 5 years of alcoholism but normal liver function tests and to correlate the findings with the possible pathophysiological basis.

MATERIALS AND METHODS

Autonomic functions were tested in apparently healthy individuals with more than 5 years of alcoholism, with normal liver function tests. Age- and sex-matched healthy non-alcoholics with normal liver function test were selected as control group.

Inclusion Criteria

Thirty, apparently healthy males of age group 20–50 years with a history of heavy alcohol intake (admitted daily consumption of ≥6 drinks or >90 ml daily)[4] for more than 5 years and with normal liver function tests and 30 age- and sex-matched normal healthy non-alcoholics with normal liver function tests were included in the study. Informed consent was taken from each subject before the commencement of the study.

Exclusion Criteria

Female and male individuals <20 years and >50 years were excluded. Furthermore, individuals with infections such as tuberculosis, malignancies (Hodgkin disease), chronic diseases (diabetes mellitus, renal failure, and amyloidosis), and other diseases which are known to interfere with autonomic functions were screened and excluded frm the study. In addition, patients with hypertension, ischemic heart diseases, congestive cardiac failure, valvular heart diseases, cardiomyopathy, and cardiac arrhythmias; patients with neurological diseases such as multiple sclerosis and Guillain–Barre syndrome; and patients on medications those were known to cause autonomic dysfunctions including diuretics, antiarrhythmic, antihypertensive, neuroleptics, and antiepileptic drugs were excluded in the study.

Study Design

Method of collection of data

After considering the inclusion and exclusion criteria, the study groups were selected. The subjects were explained about the autonomic function tests which have to be assessed, in their vernacular language, and consent is taken. Instructions were given to the subject before each parameter/component is assessed. The results were tabulated for analysis.

Materials

Sphygmomanometer, stethoscope, handgrip dynamometer, and electrocardiograph (ECG) machine were used.

Method

Tests assessed in this study were the following:

For Sympathetic Functions

BP response to standing

The BP of the subject is measured with a sphygmomanometer while he is in supine posture and again when he stands up. The postural fall in BP was taken as the difference between the systolic BP (in supine and standing positions).[5]

BP response to handgrip test

Using a handgrip dynamometer, the maximum voluntary contraction was determined first. Handgrip was then maintained at 30% of that of maximum value as long as possible for the subject up to 5 min. BP was measured 3 times before doing the maneuver and at every 1-min interval during handgrip. The result was expressed as the difference between the highest diastolic BP during handgrip exercise and the mean of the three diastolic BP readings before the handgrip maneuver.[5]

Mental stress (arithmetic) test

This test was performed by asking the subject to do serial subtraction (usually 100−7 or 1000−13). This can activate sympathetic outflow. The subsequent increase in systolic BP is measured. This should ideally exceed 10 mmHg.[6]

For Parasympathetic Functions

Resting HR

Resting HR was recorded in supine position using an ECG.

30:15 Pulse ratio (Immediate HR response to standing)

While getting up from supine to standing, a characteristic immediate rapid increase in HR occurs, which is maximal at about the 15th beat after standing, and then occurs a relative overshoot bradycardia which is maximal at about the 30th beat.

Make the subject lie supine on a couch and the HR is recorded continuously on an ECG. The subject was then asked to stand up unaided, and the point at which the subject started to stand was marked on the ECG. The shortest R-R interval at or around the 15th beat and the longest R-R interval at around the 30th beat after starting to stand were measured. The characteristic HR response was expressed by the 30:15 ratios.[5]

Expiration/inspiration ratio

The subject was asked to breathe deeply at a rate of six breaths per minute. A standard ECG recording was taken during deep inspiration and expiration. Variation in HR was calculated as the rate of the longest R-R interval during expiration to the shortest R-R interval during inspiration. A value of 1.20 or higher was taken as normal.[7]

HR (R-R interval) variation during deep breathing

ECG was recorded continuously while the subject was made to sit quietly and breathe deeply at six breaths a minute (5 s in and 5 s out) for 1 min. Onset of each inspiration and expiration was marked, and the difference in R-R interval (maximum R-R interval–minimum R-R interval) was calculated.[5]

HR response to Valsalva maneuver

Ask the subject to blow into a mouthpiece connected to a modified sphygmomanometer and hold it at a pressure of 40 mmHg for 15 s while a continuous ECG was recorded during this maneuver. This was performed 3 times with 1-min interval in between. The result was expressed as the Valsalva ratio, which is the ratio of the longest R-R interval after the maneuver (the overshoot bradycardia following release) to the shortest R-R interval during the maneuver (the tachycardia during strain). Ratio >1.21 is normal.[5]

Statistical Analysis

Student's *t*-test was used to analyze the data. Sympathetic and parasympathetic tests were conducted, and the data obtained for controls and study subjects were analyzed using Graphpad software to compare the different data. $P < 0.01$ was considered as statistically significant in this study.

RESULT

In this study, we assessed the autonomic functions in study subjects and compared their autonomic status with that of age- and sex-matched controls. The main clinical characteristics related to autonomic functions in the study subjects and the control groups are presented in this section. The results of sympathetic and parasympathetic function tests are summarized in Tables 1 and 2, respectively.

In this study, the parasympathetic function tests in alcoholics were within the normal expected range except for the resting HR which showed a significant increase in the study subjects compared with that of the controls. Sympathetic tests showed a very significant increase in BP in response to postural change and a significant change in the BP response to handgrip test.

Table 1: Sympathetic functions in control and study group individuals

Tests	Control	Study subjects
BP response to standing (mm Hg)	6±1.41421	9.2±1.09545*
BP response to sustained handgrip (mm Hg)	16.4±0.89443	11.2±1.78885*
Mental stress arithmetic test (mm Hg)	10.8±1.09545	10±1.41421

Data expressed as mean±SD, (n=30), *significant (P<0.01).
SD: Standard deviation, BP: Blood pressure

Table 2: Parasympathetic functions in control and study group individuals

Tests	Control	Study subjects
Resting HR (beats/min)	72.8±3.3466	82.8±1.0954*
30:15 pulse ratio	1.214±0.0503	1.346±0.08503
Expiration/Inspiration ratio	0.776±0.0378	0.736±0.04037
HR (R-R interval) variation during deep breathing (beats/min)	19.6±2.996	27.6±6.841
HR response to Valsalva maneuver (Valsalva ratio)	1.236±0.04827	1.226±0.02302

Data expressed as mean±SD, (n=30), *significant (P<0.01).
HR: Heart rate, SD: Standard deviation

DISCUSSION

Cardiovascular autonomic function tests have been widely used to assess the sympathetic and parasympathetic functions in different diseases.

There are at least 3 mechanisms by which alcohol may result in cardiac dysfunction. It can be direct toxic effect of alcohol or its metabolites or due to accompanying nutritional or vitamin deficiency or due to toxic effects of alcohol additives like Cobalt.[8]

Initial effects of alcohol are highly dose dependent. At lower doses, it can cause an increase in stroke volume as well as cardiac output due to sympathetic stimulation and subsequent increased circulating catecholamine.[9] At higher doses, it can cause peripheral vasodilatation which leads to fall in BP and thus a compensatory increase in HR. Increase in HR is due to centrally mediated sympathoexcitatory and vagolytic actions.[10]

In the present study, we conducted and compared the autonomic function tests in the study subjects with age- and

sex-matched controls. In our study, parasympathetic functions such as 30:15 pulse ratio, expiration/inspiration ratio, R-R interval variation during deep breathing, and HR response to Valsalva maneuver were normal except for the resting HR, which increased significantly in study subjects compared to controls.

A previous study conducted by Montforte *et al*. on 107 alcoholic patients and 61 controls found that 26 patients (24.3%) had autonomic neuropathy and 34 had peripheral neuropathy. They concluded that autonomic and peripheral neuropathies are common among alcoholic patients and suggested that alcohol appears to be toxic to autonomic and peripheral nerves in a dose-dependent manner.[11]

A similar study by Matikainen *et al*., on 28 male alcoholics, revealed that slight abnormalities were noticed in 8 patients, but a frank clinical polyneuropathy supported by neurophysiological findings could be diagnosed in only 2. All of the parameters which reflect the function of the parasympathetic division of the autonomic nervous system were lower in the alcoholics compared with controls. The most sensitive variables were the HR and the postural pulse reaction. The functions mediated by sympathetic nervous system were not abnormal among this group of alcoholics.[12]

Our observation in the present study, i.e., increase in the resting HR in alcoholics may suggest that there is some parasympathetic dysfunction, where parasympathetic tone might have decreased in these patients.

It is observed in previous studies that skin conductance and HR increased more after the alcoholic treatment compared to the non-alcoholic treatment and stayed higher until 1 h after consumption.[13] Another study reveals that alcohol reduces cardiac vagal tone and demonstrated that alcohol produces a dysregulated state in which HR is relatively uncoupled from vagal activity.[14] It is also observed that diminished vagal activity is linked to lower NO release, expected after heavy drinking and stronger reduction in vagal activity also found with chronic alcohol abuse.[15]

In the present study, it is observed that the sympathetic function tests–mental stress arithmetic test were essentially normal in both the groups. However, the study subjects showed a greater fall in the systolic BP in postural change compared to controls, which was significant. Orthostatism and head up tilt up to 65° can be used to assess the presence of postural hypotension, defined as a fall of more than 20 mmHg in systolic BP on standing. This may be due to sympathetic overactivity.[16]

It is observed that some chronic alcoholics may have neuropathy involving sympathetic nerves, and this can result in distal sweating loss and occasionally in orthostatic hypotension.[17]

A study conducted by Narkiewicz *et al*. concluded that short-term alcohol consumption elicits hypotension during orthostatic stress due to attenuation of sympathetic vasoconstrictor response.[18]

Similarly, in the present study, it is observed that the BP response to handgrip test has significantly altered in the study subjects compared to controls where expected rise in the diastolic BP was not seen in the study subjects compared to the controls.

The previous study conducted by Howes and Reid concluded that regular alcohol consumption attenuated the rise in the BP during isometric exercises due to decrease in the adrenoceptor mediated cardiovascular activity.[19]

These observations show that alcohol exerts its direct toxic effect on both the parasympathetic and sympathetic functions even without and before the involvement of liver.

We have taken $P < 0.01$ instead of 0.05 as significant in this study to make the results more accurate.

We have tested the autonomic function tests manually with whatever infrastructure available in the department, not used any digitalized instruments to calculate it.

CONCLUSION

Resting HR as well as BP response to posture change and handgrip test showed a significant change in the study subjects compared to controls which suggest that both sympathetic and parasympathetic tests are altered. We will conclude this study with the findings that alcohol has a direct effect on the autonomic nervous system even when the liver function tests are not altered.

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