Original paper

Evaluation of Cardiovascular Autonomic Dysfunction in Chronic Viral Hepatitis in Untreated Patients

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Abstract

Background: The autonomic nervous system plays a major role in the regulation of the cardiovascular system under both physiological and pathological conditions, Subclinical autonomic dysfunction can, however, occur within a year of diagnosis, and impaired autonomic function has been described in patients with chronic liver diseases from different etiologies, the chronic viral hepatitis (CVH) is the principal cause of chronic liver disease. Patients with CVH have many extrahepatic manifestations, and even with no clear evidence of autonomic nervous system dysfunction. Consequently, the purpose of this study/ to evaluate the cardiovascular autonomic dysfunction in such patients.

Method: Sixty two CVH patients include in this study, (36 patients have CVH B and 26 patients have CVHC), compared with thirty normal, healthy control group in analysis of heart rate, including heart rate in postural change, in deep breathing and valsalva maneuver, and the parameter of blood pressure in the supine position, response to postural change, isometric handgrip.

Result: The results point out to both parasympathetic and sympathetic efferent fibers modulates cardiovascular function is affected, it has been found cardiac autonomic dysfunction in analysis of results recorded in 55.56% of CVHB patients from these percentage 50% patients had subclinical cardiac autonomic dysfunction and 50% had mild clinical cardiovascular autonomic dysfunction, while the CVHC patients 69.23% had cardiovascular autonomic dysfunction, from these percentage 44.44% patients had subclinical cardiac autonomic dysfunction, and 55,56% had mild clinical cardiovascular autonomic dysfunction.

Conclusion: The cardiovascular autonomic neuropathy recorded in patients with CVH, remains mild clinical or subclinical and explained by autonomic function tests.

Keywords: ANS; autonomic nervous system, CVAFT; cardiovascular cardiac autonomic function test, CVH; chronic viral hepatitis, CVHB; chronic viral hepatitis B, CVHC; chronic viral hepatitis C.

Introduction

The autonomic nervous system may help to understand the hepato-cardiac relationship, which can be classified into the liver diseases affecting the heart, the heart diseases affecting the liver, and conditions affecting the both systems at the same time [(1)]. The autonomic nervous system modulates most of the cardiovascular functions [(2)], which brings on a major part in the rule under both physiological and diseased conditions [(3)]. The physiological responses of the sympathetic nervous system stimulation are increased heart rate and blood pressure; while the physiological responses of the parasympathetic stimulation decrease heart rate, contractility and vasodilatation [(4, 5)]. In addition to the regulation, the autonomic nervous system is involved in energy metabolism in the cardiovascular system [(6)].

The cardiovascular autonomic neuropathy is the most clinically important because of its association with a variety of

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adverse effects, including cardiovascular deaths [7]. The sudden unexpected deaths among subjects identified with autonomic neuropathy reported in a number of researchers [8]. The asymptomatic ischemia, eventually inducing lethal arrhythmias is a example of sudden death [7].

Autonomic neuropathy may also be considered as a potential etiologic factor of hyperdynamic circulation and portal hypertension [10]. Impaired autonomic functions has been described in patients with chronic liver disease from different etiologies, subclinical autonomic dysfunction can, nevertheless, pass off within a year of diagnosis chronic liver disease, and has turned out to be a poor prognostic indicator [11]. However, the presence of autonomic neuropathy in chronic liver diseases has been examined and proven by several studies [10].

The Chronic viral hepatitis is the principal reason of chronic liver disease [12], Patients with chronic viral hepatitis infection frequently have many extrahepatic manifestations, neurological complications are normally happening in a large number of patients, including impairment of both peripheral and central nervous system [13]. Neurological complications are range from peripheral neuropathy to cognitive damage, and not clearly; autonomic nervous system dysfunction, this tie of both parasympathetic and sympathetic efferent cardiovascular dysfunction as the extrahepatic manifestations of chronic viral hepatitis [14]

A non-invasive, programmable cardiovascular monitoring system for performing autonomic nervous system function tests by monitoring and analyzing ECG signals in relation to specific paced breathing and/or posture regimens exists. Such tests are currently being performed manually and/or with multiple components, and have sufficient accuracy to discriminate between normal and abnormal ECG signals, and to edit the automated test results to enhance their validity, heart rate variability measures are an important means of determining cardiac autonomic function [9] The aim of this study to assess the cardiovascular autonomic function test and evaluate the relationship between these tests to diagnosis the early sign of cardiovascular dysfunction in chronic viral hepatitis.

Materials and Methods

Sixty two patients are included in this study 36 patients have chronic viral hepatitis type B (26 male and 10 female) with the age of (40.6 ± 10.8 years) and 26 patients have chronic viral hepatitis type C (22 male and 4 female) with the age of (41.4 ± 8.4 years), all patients included in this survey were selected according to the criteria as:

1.Not received treatment for this disease.
2.Not tea at period of examination, No coffee, and smoking.
3.Exclude the alcoholism
4.Patients with diabetes, kidney disease as uremia, alcoholic abuse, and nutrition or lipid metabolism disorders were selected away.

Thirty healthy control group were admitted (20 male & 10 females), with an age of (39.52 ± 5.37 years). The study was carried on during the period from January 2009 in the Iraqi hepatic center, till the March 2010.

All subject group of the present study; investigate the current study tests the hypothesis that autonomic function--as measured by heart rate in supine position and responses to the Valsalva maneuver ((Exhale forcefully in to the manometer with close the nose by the clips and control the pressure in the sphygmomanometer at 50mm of Hg for 15 sec, Record the ECG 20 to 40 sec before, during the procedure, during the maneuver explain four phase of changes in heart rate, measuring a Longest RR in phase I/ Shortest RR in phase III, while by the blood pressure measurement repeated the maneuver to explain the different between the phase II and phase

IV)). And 30:15 electrocardiogram (ECG) R-R interval to upright position (postural ratio).

In the deep breathing measuring the heart rate, with the patients lying down comfortably, deep slowly breathing we taught the patients (to count the breaths in, 1 – 2 – 3 – 4 – 5, and breathe out, – 1 – 2 – 3 – 4 – 5 and so on) about 6 breaths per min, 5 minutes each for inspiration and expiration, measuring the ratio of the longest RR interval (Expiration): Shortest RR interval (Inspiration).

Measurement the BP in the supine position and suddenly standing position from zero to the 1st and 2nd minutes the blood pressure was assessed. Supine blood pressure levels and the lowest erect blood pressure levels (both systolic and diastolic), and differences in systolic
Blood pressure (SBP) levels and diastolic blood pressure (DBP) levels were computed and the obtained values were documented in mm Hg. The patients performed the effort capacity of the hand grip at 30% maintain maximum voluntary contraction (MVC) for at least 60 minutes. BP was monitored in the non-exercising arm after 1 minute of sustained handgrip for 5 minutes, blood pressures were evaluated. After that we asked the subject to discontinue the practice session and recorded BP at once. Statistical analysis was performed with an SPSS package (version 20).

Result

The CVH type B and C patients evaluated by clinical examination, we found 20 patients, 10 patients from each patient group received the sign and symptom of cardiovascular dysfunction include:

1. **Orthostatic hypotension/ defined as postural hypotension is a drop in blood pressure (i.e.,** Systolic >20 mm Hg or diastolic >10 mm Hg in blood pressure) with response to positional change, with Symptoms such as dizziness, weakness, fatigue, visual blurring and Visual darkening.
2. **Mild Exercise intolerance/** Autonomic dysfunction can impair exercise tolerance, reduced response in heart rate and blood pressure during exercise in individuals)).

The parameters of the autonomic function analysis test in the patients group and control group including:

1. In supine position measured the BP and HR of the patients
2. By the ECG calculate the HR response to postural change (30:15 pastoral ratio)
3. By the ECG calculate the HR during deep breathing variation of longest RR interval (Expiration): Shortest RR interval (Inspiration) {E: I}
4. R and BP response to four phases of Valsalva Maneuver (VR Ratio of heart rate (Longest RR in phase IV: Shortest RR in phase II) and blood pressure response in phase II and phase IV)
5. P response to postural change
6. P response to sustained isometric handgrip

In these works there is recorded disturbance in heart rate during supine position, remaining firm, deep breathing Long RR E: I short RR ratio, Valsalva maneuver L/S RR ratio and 30:15 ratio is indicative of the overall status of the Autonomic nervous fibers, analysis of these parameters in the CVH patients with the normal values of the control group and were calculated the mean with SD and the main difference with the control is significant at the 0.05 level ($P \leq 0.05$) are illustrated in table1.

The parameter findings of blood pressure in autonomic function tests showed the statistical difference percentage in the number of patients with hypertension and hypotension in comfortable lying, postural change, Valsalva maneuver and sustained isometric handgrip of both type B and type C chronic viral hepatitis patients in comparison with control group were

calculated the mean with SD are illustrated in table2.

The correlation between the heart rate and blood pressure in response to a different position and exercise explain the result of tests in patients with CVH had cardiovascular autonomic dysfunction or not, showing in some patients affected by different positive responses at the same time, these findings are illustrated in table3

Table1. Heart rate, significantly in relation to the control group

Parameter of H R	Subject	No.	HR in supine	HR with Postural changes	postural 30:15 Ratio	HR with VM [L:S RR]	Deep Breathing [long RR E:I short RR]
Mean ± SD	CVHB	36	89.0 ± 6.08	82.44 ± 7.28	1.49 ± 0.17	1.22 ± 0.050	1.178± .0165
	CVHC	26	83.61 ± 10.21	82.30 ± 9.96	1.45 ± 0.17	1.21± 0.080	1.184 ± .0176
	Control	30	79.10 ± 3.78	77.2 ± 2.3	1.70 ± 0.01	1.07 ± 0.077	1.044 ± 0.103
P-value	CVHB		0.05 S	0.06 NS	0.001 S	0.00 S	0.00 S
	CVHC		0.07 NS	0.06 NS	0.004 S	0.00 S	0.00 S

The mean difference with the control is significant at the 0.05 level ($P \leq 0.05$). S = Significant NS= Non significant
[L:S RR] = (VR Ratio of heart rate (Longest RR in phase IV/ Shortest RR in phase II))
Long RR E: I short RR] = breathing longest RR interval (Expiration)/ Shortest RR interval (Inspiration)

Table 2. Blood pressure changes

Position response	Parameter of BP	CVHB	CVHC	Control
No.		36	26	30
Comfortable in supine	Systolic BP Mean ± SD	119.17 ± 16.6	120.77 ± 13.2	120.75 ± 2.44
	Diastolic BP Mean ± SD	73.6 ± 23.04	81.9 ± 11.46	76.75 ± 4.67
	*↑ BP Count %	4 11.11%	6 23.08%	0 0%
	*↓BP Count %	4 11.11%	6 23.08%	0 0%
Postural change	Systolic BP Mean ± SD	114.7 ± 18.6	112.3 ± 20.1	118.75 ± 2.22
	Diastolic BP Mean ± SD	70.1 ± 12.3	69.8 ± 17.8	74.25 ± 4.94
	↑ BP Count %	4 11.11%	4 15.38%	0 0%
	↓ BP Count %	16 44.44%	15 57.69%	2 6.67%
Sustained isometric handgrip	Systolic BP Mean ± SD	136.67 ± 14.95	129.08 ± 16	123.5 ± 3.66
	Diastolic BP Mean ± SD	86.9 ± 14.15	90 ± 17.5	80.75 ± 3.72
	↑ BP Count %	18 50%	16 61.54%	2 6.67%
	↓BP Count %	8 22.22%	8 30.77%	0 0%
Valsalva Maneuver	Systolic BP Mean ± SD	139.67 ± 18.90	139.08 ± 10	133.6 ± 1.68
	Diastolic BP Mean ± SD	96.9 ± 10.12	97 ± 17	90.55 ± 8.42
	↑BP in Phase I Count %	22 61.11%	16 61.54 %	15 50%
	↑BP in Phase III Count %	18 50 %	14 53.85 %	1 3.33%

*↑ BP= increase blood pressure (mild hypertension)
*↓ BP= decrease blood pressure (mild hypotension)

Table3. Percentage of cardiovascular autonomic dysfunction

Type of virus	No.	Count & %	Normal	Subclinical ACD	Clinical ACD*	Total Patient with ACD
B virus	36	Count	16	10	10	20
	100%	% of affect	44.44%	27.78%	27.78%	55.56%
C virus	26	Count	8	8	10	18
	100%	% of affect	30.77%	30.77%	38.46%	69.23%
Total	62	Count	24	18	20	38
	100%	% of affect	38.71%	29.03%	32.26%	61.29%

*__ACD__ = Autonomic cardiovascular dysfunction

*__Clinical ACD__ // clinical autonomic cardiovascular dysfunction

Discussion

Many systemic diseases are related to causes of cardiovascular autonomic dysfunction, we have applied is an indirect way to analyze cardiovascular autonomic function tests, this study revealed an increased prevalence of abnormal blood pressure and heart rates during the cardiac autonomic function tests.

Subclinical cardiovascular dysfunction results from mild damage or isolated to the sympathetic and parasympathetic nerve fibers that innervate the cardiac muscles and blood vessels and results in abnormalities of the heart rate and vascular dynamics. Reduced heart rate variation is the earliest indicator of mild cardiovascular autonomic dysfunction [(21)].

Generally; Our results point out to both parasympathetic and sympathetic efferent cardiovascular function is affected, it has been found cardiac autonomic dysfunction in analysis of results recorded in 55.56% of CVHB patients from these percentage 50% (27.78% of total CVHB patients) had subclinical cardiac autonomic dysfunction and 50% had mild clinical cardiovascular autonomic dysfunction, while the CVHC patients 69.23% had cardiovascular autonomic dysfunction, from these percentage 44.44% (30.77% of total CVHB patients) had subclinical cardiac autonomic dysfunction, and 55,56% (38.46% of total CVHB patients) had mild clinical cardiovascular autonomic dysfunction (18, 19, 22, 26).

The increases its predictive value when there are more than three abnormal tests are obtained, the influence of cardiogenic autonomic dysfunction explained by assessed via heart rate variation, the ratio of the R-R intervals of the thirtieth and the fifteenth heart beat (30:15) after standing and R-R variation of Valsalva ratio was lower in the patients; these are commonly used to quantitatively assess autonomic neuropathy to assess the sensitivity of these two measures to parasympathetic ablation, we found statistically highly significant difference in the standing (30:15) and Valsalva ratio (Longest RR in phase IV: Shortest RR in phase II) ratio and during deep breathing longest RR interval (Expiration): Shortest RR interval (Inspiration) {E: I ratio} in compare with control group, while the blood pressure response to standing, recorded high percentage on number of patient with hypertension in Phase 1 and continuous with phase IV during the Valsalva Maneuver, and Sustained isometric handgrip recorded disturbance in percentage of hypertension and hypotension. The relationship between cardiovascular autonomic dysfunction and major cardiovascular events has been assessed the subsequent incidence of a fatal or nonfatal event to CVS, defined as an ischemic attack, heart failure, and resuscitation from ventricular tachycardia or fibrillation, these relationship are explained by other authors (6, 23, 24) and this disorder results from disorder of the autonomic nerve fibers with associated abnormalities of heart rate control and vascular dynamics. The daily activities of patients with cardiovascular autonomic dysfunction can produce troubling symptoms cause's lethal outcomes (e.g., Syncope).

Some authors reported these changes of cardiovascular autonomic dysfunction in patients with chronic Hepatitis C Virus infection only during antiviral drug therapy [15,16, 25] so this may be related to the antivirus drug therapy is exaggerated to these mild subclinical events of cardiovascular autonomic dysfunction, we reported these changes mild or subclinical not appear with first time.

Conclusion

The cardiovascular autonomic neuropathy (cardiac autonomic dysfunction) recorded in patients with chronic viral hepatitis, remains mild clinical or subclinical and explained by autonomic function tests. The subclinical cardiovascular autonomic neuropath recording more significant in chronic viral hepatitis type B while the chronic viral hepatitis type C had more percent of the mild clinical autonomic dysfunction.

Recommendations

The use of autonomic function tests favor a true incidence of autonomic nervous system involvement in Chronic Viral Hepatitis patient, and more accurate diagnosis which leads to a better clinical care before the development of the cardiac autonomic dysfunction.

1. Autonomic function tests as a follow up investigation monthly to exclude the autonomic nervous system abnormality before the patients take therapy and after, for explained the relationship of autonomic dysfunction with or without medication.
2. Additional type of autonomic function test studies in this article may be necessary to detect subclinical dysfunction involvement.

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