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Assessment of sympathovagal balance by HRV analysis in alcoholic and nonalcoholic fatty liver disease patients

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Abstract:

BACKGROUND: Heart rate variability (HRV) is the variation in the time intervals between continuous heartbeats also called interbeat intervals to give information related to the heart, blood pressure, gaseous exchange, and sympathetic and parasympathetic balance. Abnormalities in the conduction of the cardiac system alter the measurements of heart rate variability and lead to alteration in autonomic function with a higher risk of mortality. So, our objective includes the assessment of sympathovagal balance in AFLD and NAFLD patients.

MATERIALS AND METHODS: The study included 78 alcoholic and 54 nonalcoholic fatty liver patients. A room temperature of 23°C with 25–35% humidity will be maintained in a recording room. Basal supine heart rate and BP will be recorded by the oscillometric method using an automated blood pressure monitor Omron MX3, India. Lead II ECG will be recorded for the next 5 minutes in total resting condition for short-term HRV analysis. Short-term HRV indices including time domain and frequency domain were recorded from each patient. Under time domain, SDNN, RMSSD, and average RR were noted. Under frequency domain, LF, HF, VLF, LF (nu), HF (nu), and LF/HF were calculated. The data were collected by using a 16-bit, power lab 8/30 data acquisition system (New South Wales, Australia) with acknowledge 3.8.2 software. Inferential analyses such as independent t-tests and Mann–Whitney tests were used to compare NAFLD and AFLD patient groups. Carl Pearson correlation analysis was performed to obtain a relationship between variables.

RESULTS: SDNN in (ms) which represents the overall HRV found to be decreased in both alcoholic (32.84 ± 79.08) and nonalcoholic fatty liver disease (22.04 ± 13.85) compared to the normal range (50 ± 16)) from 27 studies. The value of RMSSD in (ms) was decreased in both alcoholic (17.00 ± 12.48) and nonalcoholic fatty liver disease patients (14.00 ± 9.44) with the normal range of (42 ± 15) from 15 studies. Pearson correlation analysis showed the age of AFLD patients significantly and positively correlated with average RR. Pearson correlation analysis for the age of NAFLD patients was significantly and positively correlated with the average RR, HF, SDNN, RMSSD, and LF.

CONCLUSION: Altered autonomic activity was noted in both alcoholic and nonalcoholic fatty liver disease patients. An early prognosis of fatty liver is very necessary to prevent the disease progress into later fatal life-threatening stages.

Keywords:

Alcoholic, Autonomic nervous system, Fatty liver, Nonalcoholic fatty liver disease, Parasympathetic nervous system, Sympathetic nervous system

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Introduction

Heart rate variability (HRV) is defined as the fluctuation in the beat-to-beat intervals of the heart, which gives the interaction between sympathetic and parasympathetic nervous systems that helps to evaluate the imbalance in the autonomic nervous system.[1] HRV is widely used

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to analyze cardiac autonomic function because of its high repeatability and is noninvasive.[2,3] Consuming large amounts of alcohol, even for just a few days, can lead to the storage of fat in the liver termed alcoholic fatty liver.[4] Fatty liver is an important warning sign for drinking at a harmful level, but it rarely causes any symptoms. Consumption of alcohol alters metabolic function as well as it also causes tissue damage. Alcoholic fatty liver disease is one of the most frequent liver diseases, affecting millions of people worldwide; it can progress to liver cirrhosis and fatal liver carcinoma.[5] Nonalcoholic fatty liver disease (NAFLD) is a clinical pathological condition characterized by the collection of extra fat in the liver that is not caused by alcohol.[6] NAFLD may cause swelling of the liver (steatohepatitis), and this may cause cirrhosis and may even lead to liver cancer or liver failure. NAFLD develops in people who are overweight or obese and have elevated levels of triglycerides or cholesterol. Poor eating patterns and rapid weight loss may also lead to NAFLD. NAFLD is closely linked with hypertension, hyperglycemia, central obesity, and dyslipidemia.[7] Hypertension leads to hypertensive heart disease, and it is considered the main cause of death linked to hypertension.[8] A reduced HRV is always associated with cardiovascular dysfunction, resulting in cardiovascular morbidity and mortality. To the best of our knowledge, there are very few studies on the autonomic status of AFLD patients reported in India. In addition, we could find one study comparing the autonomic status between AFLD and NAFLD patients which included even diabetic patients. Since cardiovascular autonomic neuropathy is common in diabetic patients, we wanted to assess the sympathovagal balance in AFLD and NAFLD patients who are not diabetic. Currently, the disease burden of patients suffering from alcoholic and nonalcoholic fatty liver is increasing worldwide. So, this study will help to identify the factors responsible for autonomic imbalance and helps to suggest a way to overcome the disease burden in the future. So, this study was undertaken to assess the sympathovagal balance in alcoholic and nonalcoholic fatty liver disease patients.

Materials and Methods

Study design and setting

This perspective time-bound study for a period of 3 years included alcoholic and nonalcoholic fatty liver disease patients attending a private medical college's Department of Medicine and General Surgery. HRV analysis was conducted in the Department of Physiology of the Medical College.

Study participants and sampling

The sample size was collected based on 5% level of significance, power of 80%, at 0.5 effect size and 0.7 as a ratio (n2/n1). The minimum sample size required will be 78 for alcoholic fatty liver disease and 54 for nonalcoholic fatty liver disease. The sample size is determined using the software G*Power Version 3. This study included patients in the 35–65 age group diagnosed with alcoholic and nonalcoholic fatty liver disease by a physician. Patients consuming alcohol more than or equal to 210 grams per week in men and more than or equal to 140 grams per week in women for about long 5 years and having fatty liver confirmed by ultrasonography will be further classified as AFLD patients. Others who are nonalcoholic with fatty liver are NAFLD patients. Patients who are patients with Hepatitis B and C, HIV infections, patients with thyroid dysfunction, diabetes mellitus, and pregnant and lactating were excluded from the present study.

Data collection tool and technique

In the beginning, for about 5 minutes patients were asked to lie down in a supine position. After this 5 minutes of rest, their heart rate variability was noted by using an eight-channel power lab. All the time domain and frequency domain indices were noted from all the alcoholic and nonalcoholic fatty liver disease patients. Collected data were analyzed using descriptive and inferential statistical methods. Descriptive methods such as frequency, percentage, mean, standard deviation, confidence interval, median, and interquartile range (IQR) were used to summarize and assess the parameters. Inferential analyses such as independent t-tests and Mann–Whitney tests were used to compare NAFLD and AFLD patient groups. Carl Pearson correlation analysis was performed to obtain a relationship between variables.

Standards for heart rate variability were recommended by the Taskforce of the European Cardiology Society and the North American Society of Pacing and Electrophysiology, so HRV is performed by both frequency domain and time domain indices.[1] Frequency domain analysis helps to understand the autonomic changes in the RR interval of the recording of the heart rate. SDNN in time domain indices represents the autonomic modulation of overall activity, whereas RMSSD represents the cardiac parasympathetic activity. For the measurement of frequency domain indices, low frequency (LF), high frequency (HF), a normalized unit of LF, and HF are analyzed. LF represents the sympathetic activity, and HF represents the parasympathetic activity of the sinus node. LF/HF ratio represents sympathovagal balance in heart rate variability analysis.[9]

Ethical consideration

Ethical clearance was obtained from the Institute's Ethics Committee (protocol no 2019/079) for the study. Written informed consent was taken from all the patients before the commencement of the study.

Results

The time domain and frequency domain indices of heart rate variability was calculated from all included patients. To compare heart rate variability between alcoholic and nonalcoholic fatty liver disease, an independent *t*-test was performed for average RR, LF (nu), HF, and HF (nu), whereas Mann–Whitney test was performed for SDNN, RMSSD, LF, and LF/HF. According to the independent *t*-test, [Table 1] the average RR was 767.56 ± 83.05 in the AFLD group, and it was 774 ± 123.97 in the NAFLD group. The test shows that there is no significant difference between AFLD and NAFLD groups with respect to average RR. High frequency (HF) was 174.52 ± 312 in the alcoholic and 97.85 ± 127.97 in the NAFLD group. The test shows that there is no significant difference between AFLD and NAFLD groups with respect to HF. LFnu was 51.65 ± 18.74 in the AFLD group and it was 47.37 ± 22.67 in NAFLD. This test shows that there is no significant difference between AFLD and NAFLD groups with respect to LFnu. HFnu was 43.28 ± 18.23 in the AFLD group, and it was 45.71 ± 21.73 in the NAFLD group. This test shows that there is no significant difference between AFLD and NAFLD groups with respect to HFnu.

A correlation of the age of alcoholic and nonalcoholic fatty liver disease patients with HRV parameters was performed. In Table 2, Pearson correlation analysis for alcoholic fatty liver disease patients showed that the age of AFLD patients significantly and positively correlated with average RR. But the age of the AFLD patient has no significant correlation with HF, LF (nu), (HF (nu), SDNN, RMSSD, LF, and LF/HF. Pearson correlation analysis for nonalcoholic fatty liver disease showed that the age of NAFLD patients was significantly and positively correlated with the average RR, HF, SDNN, RMSSD, and LF. However, the age of NAFLD patients has no significant correlation with LF (nu), HF (nu), and LF/HF.

Discussion

This study was conducted to assess and compare the autonomic function between AFLD and NAFLD patients. In this study, it was found that the SDNN value that represents the overall autonomic modulation was found to be decreased than normal in both alcoholic and nonalcoholic fatty liver disease. RMSSD which represents the cardiac parasympathetic activity also found to be decreased than normal in both alcoholic and nonalcoholic fatty liver disease patients. Previous studies reported that lower values of RMSSD or SDNN are associated with higher risks for cardiovascular morbidity and mortality.[10] Also studies have reported that reduced SDNN in HRV analysis is associated with increased overall activity and cardiovascular-related mortality in the general population.[11] Decreased heart rate variability reflects the imbalance in autonomic function.[12] Earlier studies have concluded that decreased HRV is directly associated with cardiometabolic risk factors leading to

Table 1: Comparison of heart rate variability (HRV analysis) between alcoholic and nonalcoholic fatty liver disease

HRV analysis	Patient group [AFLD-78 NAFLD-54]	Mean±SD	95% confidence interval for the mean		*t*-test	*P*
			Lower	Upper		
Average RR	AFLD	767.56±83.05	748.83	786.28	-0.389	0.698
	NAFLD	774.56±123.97	740.72	808.40		
LF (nu)	AFLD	51.65±18.74	47.42	55.87	1.182	0.240
	NAFLD	47.37±22.67	41.19	53.56		
HF (Hz)	AFLD	174.52±312.00	101.18	244.87	1.708	0.090
	NAFLD	97.85±127.97	62.92	132.78		
HF (nu)	AFLD	43.28±18.23	39.17	47.39	-0.704	0.483
	NAFLD	45.71±21.13	39.94	51.47		
HRV Analysis	**Patient group**	**Mean±SD**	**Median**	**IQR**		**Mann–Whitney test *Z***	***P***
				Lower	**Upper**		
SDNN (ms)	AFLD	32.84±79.08	21.50	14.90	31.14	-1.248	0.212
	NAFLD	22.04±13.85	19.08	11.22	28.65		
RMSSD(ms)	AFLD	17.00±12.48	13.81	9.16	20.95	-1.044	0.297
	NAFLD	14.00±9.44	13.57	6.06	18.59		
VLF (Hz)	AFLD	279.78±362.42	252.25	117.48	319.20	-0.264	0.792
	NAFLD	268.53±270.37	176.80	53.23	354.40		
LF (Hz)	AFLD	178.89±250.11	108.00	32.67	231.00	-1.553	0.120
	NAFLD	139.09±206.18	60.13	16.25	155.30		
LF/HF	AFLD	2.04±2.28	1.02	0.72	2.15	-1.382	0.167
	NAFLD	1.80±1.96	0.88	0.36	2.48		

[HRV—heart rate variability, n=no. of patients, SD—standard deviation, average RR—average of all intervals, SDNN—standard deviation of NN interval, LF—low frequency, HF—high frequency, LFnu, HFnu—low-frequency and high-frequency powers of heart rate variability expressed in normal units, RMSSD—reflects of beat-to-beat variance, LF/HF—low frequency: high frequency, Hz—Hertz, ms—milliseconds]

Table 2: Correlation of age of alcoholic and nonalcoholic fatty liver disease patients with other parameters

Group AFLD[78]	Pearson Correlation	*P*	Group NAFLD[54]	Pearson correlation	*P*
Average RR	0.318	0.005	Average RR	0.543	0.000
HF (Hz)	-0.040	0.729	HF	0.469	0.000
LF (nu)	0.028	0.805	LF (nu)	0.170	0.220
HF (nu)	-0.143	0.211	Hf (nu)	-0.122	0.380
SDNN (ms)	-0.059	0.607	SDNN	0.377	0.005
RMSSD (ms)	0.067	0.560	RMSSD	0.535	0.000
VLF (Hz)	0.111	0.332	VLF	0.463	0.000
LF (Hz)	0.016	0.890	LF	0.274	0.045
LF/HF	-0.171	0.134	LF/HF	0.099	0.435

P=0.000, <0.05 (significant). AFLD—alcoholic fatty liver disease, NAFLD—nonalcoholic fatty liver disease, SDNN—standard deviation of NN interval, RMSSD—reflects of beat-to-beat variance, LF—low frequency, LFnu, HFnu—low-frequency and high-frequency powers of heart rate variability expressed in normal units

cardiovascular morbidity and mortality.[12] Impairment of HRV increases with increasing severity of liver disease as well as autonomic dysfunction in liver disease increases the risk of mortality rate fivefold.[10] LF and HF were found to be more in alcoholic fatty liver disease than the nonalcoholic fatty liver disease patients, but it was found to be under the normal range. The increase in LF shows that the balance has shifted in favor of the sympathetic system; hence, the sympathetic system is overactive in the body.[13] Also an increased LF: HF was reported in NAFLD patients with decreased baroreflex sensitivity.[14] The normalized unit of LF (nu) was more in alcoholic fatty liver disease patients than in nonalcoholic fatty liver disease patients, but it was under the normal range. Also, normalized unit HF (nu) was found to be more in the nonalcoholic group than the alcoholic fatty liver disease patients. LF/HF represents that the sympathovagal balance was more in alcoholic fatty liver disease than the nonalcoholic fatty liver disease patients. In this present study, the autonomic imbalance is observed in both alcoholic and nonalcoholic fatty liver disease patients. An imbalanced autonomic function is suggested to be an increased risk factor for the pathogenesis of NAFLD along with that, decreased parasympathetic activity and increased sympathetic activity are also considered to be a higher risk for the development of NAFLD.[9] NAFLD is associated with cardiovascular disease progression and also be the reason for the higher number of cancer-related mortality.[15,16] Previous studies have reported that NAFLD is considered to be an independent risk factor for atherosclerosis which is directly linked to the liver disease progression.[17] One of the studies suggested that NAFLD patients should be given importance to the comorbidity of autonomic dysfunction.[18] Long duration of alcohol consumption can increase the risk for metabolic syndrome, central obesity, and cardiovascular-related disorders.[19] Studies have reported that since autonomic neuropathy is the vagal origin, autonomic damage can be expected in alcoholic liver disease patients.[20]

Conclusion

Overall autonomic modulations were found to be altered in both alcoholic and nonalcoholic fatty liver disease patients. The parasympathetic activity was also lowered in both alcoholic and nonalcoholic fatty liver disease patients. The prognosis of fatty liver progression in the early stage of NAFLD may be helpful to prevent the further development of the disease into a fatal stage. Withdrawal of alcohol in the early stages of liver disease may help to prevent the mortality rate in alcoholic patients.

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Abbreviations

HRV-	Heart rate variability
AFLD-	Alcoholic fatty liver disease
NAFLD-	Nonalcoholic fatty liver disease
SDNN-	Standard deviation of NN interval
RMSSD-	Reflects on beat-to-beat variance
LF-	Low frequency
HF-	High frequency
VLF-	Very low-frequency power
LFnu, HFnu-	Low-frequency and high-frequency powers of heart rate variability expressed in normal units
LF/HF-	Low frequency: high frequency
Hz-	Hertz
ms-	Milliseconds.

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Conflicts of interest

There are no conflicts of interest.

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