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Original Research Article

Evaluation of Parasympathetic Activity by Heart Rate Variability in Gastroesophageal Reflux Disease Patients

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Abstract: The disturbed autonomic nervous system regulation may be responsible for functional lower esophageal sphincter failure, so the present study aimed to evaluate the parasympathetic activity in patients with Gastroesophageal reflux disease by time domain measures of Heart rate variability analysis. One hundred five subjects, which include Gastroesophageal reflux disease patients, thirty five each, aged 35-45 years (who presented typical symptom of Gastroesophageal reflux disease with reflux esophagitis (ERD) and without reflux esophagitis (NERD)) and thirty five age and sex matched control subjects, were evaluated in the study. Autonomic function test were assessed by using time domain measures of Heart rate variability. The findings of the present study showed highly significant ($p < 0.001$) reduced values of SDNN, RMSSD and pNN50 in patients with Gastroesophageal reflux disease as compared to control subjects predicting reduced parasympathetic activity in patients with Gastroesophageal reflux disease. Disturbances in parasympathetic branch of autonomic nervous system affect both contraction and transient relaxation of the lower esophageal sphincter, leading to the occurrence and progression of Gastroesophageal reflux disease.
Keywords: Autonomic Nervous System, Gastroesophageal reflux disease, Time domain measures, Heart rate variability analysis.

INTRODUCTION

GERD is a highly prevalent gastrointestinal (GI) disorder, affecting the upper part of the gastrointestinal tract, and is one of the most common GI illnesses encountered in clinical practice. The incidence and prevalence of GERD are rising, it is estimated to affect 10 – 20% of the inhabitants of Western countries and 5% of Asians [1].

GERD is usually divided into two main subclasses, with mucosal inflammatory changes (esophagitis) (ERD - Erosive reflux disease) or without mucosal inflammatory changes (NERD - Non erosive reflux disease) [2]. In non-erosive reflux esophagitis (NERD), mucosa may be normal or mildly erythematous. Erosive reflux esophagitis (ERD) reveals clear mucosal damage with redness, friability, superficial linear ulcers and exudates [3].

The tonic contraction of lower esophageal sphincter (LES) is primarily responsible for preventing reflux of acidic gastric components into the esophagus [4]. The lower esophageal sphincter (LES) relaxation occurs with swallowing, but it also occurs with gastric distension, apparently by means of a different neural circuit [5]. Distension of gastric mechanoreceptors triggers transient lower esophageal sphincter relaxations (TLESRs) and this is the almost exclusive mechanism for gastroesophageal reflux in healthy persons [6, 7].

The enteric nervous system is most probably the final common pathway for LES function, but it integrates signals from autonomic nervous system [8].

Heart rate variability (HRV) tests are non-invasive methods of evaluating the integrity and functional state of the autonomic nervous system (ANS). HRV is beat to beat variation in heart rate (i.e. in R-R interval) under resting conditions. It may be carried out using the short-term or long-term recordings. Time domain and frequency domain analyses are the methods of HRV assessment. A number of variables that describe either the heart rate at any time or determine the intervals between successive normal complexes are calculated during time domain analysis. The time domain method estimates fluctuations of R - R intervals on the ECG curve [9].

In gastroesophageal reflux disease, the primary cause is not within the LES itself, but with the neural regulation of LES function. The disturbed autonomic nervous system regulation may be responsible for functional LES failure. Thus the purpose of the present study was to evaluate the parasympathetic activity in GERD patients by time domain measures of HRV analysis.

MATERIAL AND METHODS

The present study was carried out in the Upgraded Department of Physiology, S.M.S. Medical College with requisite collaboration from the Department of Gastroenterology, S.M.S. Hospital, Jaipur (Rajasthan). The study was carried out after getting formal approval from institutional ethics committee of S.M.S. Medical College, Jaipur.

The clinical assessment for the GERD was done by gastroenterologist using standard clinical protocol. Subjects having clinical symptoms of GERD were subjected to Endoscopic examination of upper gastrointestinal tract for the assessment of esophageal mucosa in Department of Gastroenterology, S.M.S. Hospital, Jaipur. Informed written consent was obtained from all the subjects included in the study.

One hundred five participants, aged 35-45 years of either sex were enrolled in the present research, which were grouped as follows:

1. GERD patients with reflux esophagitis (ERD; n=35)
2. GERD patients without reflux esophagitis (NERD; n=35)
3. Healthy Control subjects (Control; n=35)

Inclusion criteria for ERD and NERD group were: Confirmed GERD patients with and without reflux esophagitis (thirty five each) by gastroenterologist based on clinical symptoms and endoscopic findings in the age group of 35 to 45 years of either sex.

Inclusion criteria for Control were: Thirty five healthy control subjects in the age group of 35 to 45 years of either sex.

Exclusion criteria for ERD, NERD and Controls were: Any acute or chronic illness, subjects taking any medication that modulate Autonomic Nervous System activity and affect gastrointestinal motility and/or gastric acid secretion, alcoholic, smokers, tobacco chewers, stress, psychotic or demential disorders, obese and non-cooperative subjects. The control subjects, who have suffered from any upper GI tract disease, were also excluded.

The study protocol was explained to subjects before start of procedure. A detailed history regarding age, sex, height, weight, body mass index (BMI), alcoholic, smokers, tobacco chewers and resting blood pressure were taken and physical examination was done. Autonomic evaluation was carried out in the morning from 10:00 a.m. to 12:00 noon, 2 hour after a light breakfast and after familiarizing the subjects with the test procedures.

Heart Rate Variability Analysis

Parasympathetic activity was assessed by using time domain measures of HRV analysis. Heart rate variability assessment was done by 5 minutes recording ECG by RMS Polyrite D (PRD1502001) in software version 3.0.16.

For short-term analysis of HRV, ECG was recorded in supine position for 5minute after 15 minutes of rest. Recording was done in noise free room and room temperature was maintained at 24-28^{0}C. All standard limb leads were applied and the lead with upright R wave was selected for recording. The ECG signals were continuously amplified, digitized and stored in the computer for offline analysis. The procedure calculated the various parameters of Heart rate variability (HRV) in time domain measures. The detection of R wave was done by HRV software which computes R-R intervals after the R wave detection. Abnormal beats and areas of artifact were automatically and manually identified from the recording.

The Time domain measures of the Heart rate variability were calculated with the Fast fourier transform (FFT) based method. The time domain measures are based on the amount of time, in milliseconds, in the beat-to-beat intervals of the heart or from the differences between the normal beat-to-beat intervals. The following time domain variables were computed for each subject: standard deviation of all RR intervals over the selected time intervals (SDNN), root mean square of successive differences between adjacent RR intervals (RMSSD) and percentage of numbers of RR intervals with differences $\geq$ 50 ms (pNN50). SDNN estimates the overall HRV (ANS power) while RMSSD and pNN50 reflects parasympathetic (vagal) activity [9].

Statistical analysis

Data were presented as mean and Standard Error (mean ± SE). Statistical analysis was performed by using one way ANOVA (Bonferroni) test for comparisons of mean values of time domain variables between the study groups. The data was analyzed with the use of Microsoft Excel 2007 and SPSS for windows, version 16.0 (Chicago, SPSS Inc., 2007). A p value < 0.05 was considered significant at 95 % Confident Interval.

RESULTS

Table 1 lists the result of demographic data in mean ± SE and one way ANOVA p values. There was no significant difference in age, height, weight, body mass index, resting SBP and resting DBP between the study groups.

The mean values of all time domain measures of HRV showed a statistically highly significant difference ($p < 0.001$) among the three study groups on applying the one way ANOVA analysis (Table 2).

In the present study, it was observed that the mean difference of SDNN (ms), RMSSD (ms), pNN50 (%) between ERD and Control was highly significant ($p < 0.001$).The mean difference of SDNN (ms), RMSSD (ms), pNN50 (%) was also noted highly significant ($p < 0.001$, $p < 0.001$, $p = 0.001$, respectively) in between NERD and Control subjects, whereas between ERD and NERD, there was no significant difference ($p = 0.281$, $p = 1.000$, $p = 1.000$, respectively) observed for these comparisons (Table 3). The findings of the present study indicated reduced parasympathetic activity in GERD patients than in control subjects.

Table 1: Demographic data of the studied groups

Demographic data	ERD (n=35)	NERD (n=35)	Control (n=35)	ANOVA p value
Age (years)	38.86 ± 0.50	39.57 ± 0.69	39.29 ± 0.67	0.719†
Height (cm)	168.46 ± 1.05	164.00 ± 1.61	163.60 ± 2.00	0.063†
Weight (kg)	62.31 ± 1.70	60.77 ± 2.00	63.17 ± 1.57	0.624†
BMI (kg/m^2)	22.03 ± 0.63	22.59 ± 0.68	23.55 ± 0.36	0.172†
Resting SBP (mmHg)	117.37 ± 2.06	118.54 ± 2.01	120.03 ± 2.01	0.650†
Resting DBP (mmHg)	73.69 ± 1.32	74.26 ± 1.30	76.03 ± 1.82	0.517†

Values are mean ± SE, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, †p >0.05[Nonsignificant]

Table 2: Comparison of mean values of time domain measures of HRV in the Study Groups by one way ANOVA analysis

Groups	SDNN (ms)	RMSSD (ms)	pNN50 (%)	ANOVA p values
ERD	21.63 ± 1.48	15.81 ± 1.43	2.17 ± 0.64	< 0.001*
NERD	26.64 ± 1.62	18.63 ± 1.81	3.74 ± 1.44	< 0.001*
Controls	39.55 ± 2.88	35.11 ± 4.15	13.92 ± 2.89	< 0.001*

ERD: Erosive reflux disease, NERD: Non erosive disease, SDNN: Standard deviation of all RR intervals over the selected time intervals, RMSSD: Root mean square of successive differences between adjacent RR intervals, pNN50: Percentage of numbers of RR intervals with differences ≥ 50 ms, ANOVA: Analysis of variance, †p >0.05 [Nonsignificant], *p <0.05[Significant]

Table 3: Comparison of mean values of time domain measures of HRV in the Study Groups by Post Hoc Test, Bonferroni

Group	Group	SDNN (ms) p values	RMSSD (ms) p values	pNN50 (%) p values
ERD	NERD	0.281†	1.000†	1.000†
	Control	<0.001*	<0.001*	<0.001*
NERD	Control	<0.001*	<0.001*	0.001*

ERD: Erosive reflux disease, NERD: Non erosive disease, SDNN: Standard deviation of all RR intervals over the selected time intervals, RMSSD: Root mean square of successive differences between adjacent RR intervals, pNN50: Percentage of numbers of RR intervals with differences ≥ 50 ms, ANOVA: Analysis of variance, †p >0.05 [Nonsignificant], *p <0.05[Significant]

DISCUSSION

Autonomic nervous system (ANS) activity played an important role in pathogenesis of GERD. ANS regulates saliva secretion, esophageal and gastric motility, gastric juice secretion and mucosal blood flow. Its activity imbalance may lead to gastric and / or duodenal mucosa inflammation, erosions, peptic ulcers, dysphagia, gastroesophageal reflux, and motility disorders [10].

The present study demonstrated that GERD patients have reduced parasympathetic activity as compared to control subjects. The results of this study support the hypothesis that GERD patients have dysfunction of autonomic nervous system and pathophysiology of GERD have linked to disturbances in autonomic nervous system activity as reflected by significant changes in different time domain (SDNN, RMSSD and pNN50) parameters analyzed in this study.

One of the study done by Chakraborty *et al* [11] found that the existence of abnormal vagal function in 40% of examined patients raises the possibility that vagal dysfunction is important in the genesis of gastroesophageal reflux. The results of the present research are in accordance with Milovanovic *et al* [12]. They observed that all time domain measures of HRV; SDNN (ms), RMSSD (ms), pNN50%, which are the indicators of vagal activity, had significantly lower values in patients with GERD than in the control group. The study done by Lee et al [13] however noted that SDNN (ms) was not significantly different between the erosive and non-erosive groups while a significantly reduced RMSSD (ms) was observed in erosive group as compared to non-erosive group.

The tonic contraction that characterizes the muscle of LES is mainly myogenic [14]. The tone of LES is mainly under vagal (cholinergic) control [15]. The probable reason of the present findings is due to an insufficient tonic contraction of LES which is associated with Gastroesophageal reflux disease [16, 17]. The reduced parasympathetic activity is linked with increased Transient lower esophageal sphincter relaxations (TLESRs) frequency [18]. The decreased parasympathetic activity could lead to reduce myogenic control of the lower esophageal sphincter, favor lower esophageal sphincter relaxation, and thus increase the frequency of TLESRs [12].

This parasympathetic nerve dysfunction is also related to the delayed esophageal transit and abnormal peristalsis in GERD patients and therefore may be of pathologic importance in GERD [19].

CONCLUSION

In conclusion, autonomic dysfunction can be counted between the pathogenetic factors of Gastroesophageal reflux disease. The present study observed that parasympathetic activity was reduced in the presence and absence of reflux esophagitis. It has even been suggested that parasympathetic dysfunction is not just consequence of reflux esophagitis but the prime factor in the etiology of GERD. Disturbances in parasympathetic branch of autonomic nervous system affect both contraction and transient relaxation of the lower esophageal sphincter (normally acting as a reflux barrier), leading to the occurrence and progression of GERD.

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