ORIGINAL ARTICLE

Reduced Heart Rate Variability in Frequency domain in patients of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic Obstructive Pulmonary Disease is characterized by a progressive partially reversible, airflow obstruction. As the disease advances, COPD is linked with cardiac comorbidities due to disrupted functioning of autonomic nervous system. A vagally stimulated pattern of oscillations is generated between adjacent R-R intervals in electrocardiographic recording, which is known as Heart Rate Variability (HRV). In diseases influencing sympathovagal balance such as COPD, variability between R-R intervals is reduced. This produces a constant pattern of ECG, known as reduced HRV. The purpose of study was to assess and compare parameters of HRV in frequency domain in patients of COPD with healthy subjects .In this study, 69 non obese male subjects in the age range of 50-70 years were included. HRV was assessed using Holter Monitor. It was analyzed in frequency domain using KUBIOS HRV 3.3.0 STANDARD software. Spirolab III was used for Pulmonary Function Tests (PFTs).Data was analyzed by SPSS version 23. Results indicated that Median IQR for HF, comparing diseased groups was enhanced with disease severity (p value < 0.05). It was concluded that HRV reduced in COPD patients as compared to healthy in frequency domain . However with disease advancement HF which reflects vagal modulation was increased.
Keywords: Heart rate, frequency domain, pulmonary disease

INTRODUCTION

Global Initiative for Chronic Obstructive Lung Disease (GOLD) has defined COPD as an avoidable and curable disorder which is characterized by features of respiratory disease, including airflow obstruction. This chronically reduced airflow in COPD is because of pathology of both small sized airways disease and lung parenchyma[1]. COPD is very unusual in younger population below 40 years of age. Males are affected more due to higher smoking rate in men. A study in India gave a higher males prevalence (1.9%-9.4%) as compared to females (1.2%4.9%) [2]. Over about 90% of the mortalities in developing countries are because of COPD[3]. GOLD explains several elements linked with COPD. These factors are grouped into: Host factors (Alpha -1 Anti Trypsin Deficiency, Abnormal lung development and accelerated ageing).Subjection to Tobacco smoking, Occupational dusts, pollutants, infections and lower class)[1]. Pathogenesis of COPD includes inflammatory changes in small sized airways Increased number of inflammatory cells is seen. An imbalance between proteases/ antiproteases and oxidants/anti oxidants is also observed[4]. Alterations also occur in the pulmonary vessels including intimal hyperplasia and hypertrophy/hyperplasia of smooth muscle. These changes are a result of hypoxia induced vasoconstriction in later stages of the disease[5].This disease is linked with systemic inflammation. One of the sequale of this systemic involvement is cardiac autonomic dysfunction seen in COPD patients[6].

HRV is a tool to measure the particular variations in time between two adjacent beats (R-R interval)and is calculated in milliseconds[7]. HRV is an effective reflection of the various elements altering interrelation between parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS)[8].

Autonomic nervous system (ANS) gives its SNS and PSNS branches to heart. Thus, the two branches of ANS, provide a fine adjustment by acting in opposite ways on the heart in response to various stimuli. An imbalance between SNS and PSNS modulation has been manifested to be a major process in some cardiovascular diseases such as hypertension, myocardial infarction and cardiac failure[9].

HRV assessment is a safe way to measure autonomic dysfunction and is calculated through RR intervals. There are several ways to measure HRV i.e. through time and frequency domain systems, geometric indexes and non linear methods. In time domain ECG is done to assess R-R intervals. Average value of highest and lowest intervals is taken. Ectopic beats are not included and only Normal to Normal R-R intervals (N-N) are analysed. To measure HRV in frequency domain QRS complexes are transformed to Fournier spectrum which converts ECG signals to sinusoidal wave patterns of several frequencies The frequency domain is divided into high frequency (HF), low frequency(LF), very low frequency(VLF) and ultra low frequency(ULF). HF (0.15-0.4 Hz) measures vagal activity, whereas LF (0.04 - 0.15 Hz) is influenced by baroreceptor activity which in turn reflects SNS. The other two frequency domains i.e. very low frequency (0.003-0.04 Hz) and ultra low frequency (less than 0.003 Hz) also play a role in HRV through chemoregulation and thermoregulation[10]. In healthy individuals HRV manifests the vagal functioning. HRV is decreased in autonomic abnormalities as in

COPD[11]. It has been explained in literature that SA nodal excitation and respiratory modulation are minimized; the respiratory phenomenon is most probably because of an increase in residual volume (RV). Various studies have shown ventricular arrhythmias to be linked with COPD[12].

Rationale: A study done in Pakistan suggested that there is a need of population studies of HRV because it is influenced by habitats [13].The values given in a study for our healthy population were different from those in other parts of the world. However no such data is available on COPD Hence this study might help in comparing values for HRV in COPD in our population and rest of the world. This might also create awareness about HRV as a sensitive and non-invasive tool for autonomic dysfunction in diseases like COPD.

In present study, it was hypothesized that HRV reduces with a decrease in pulmonary function tests in COPD.

MATERIALS AND METHODS

It was a cross-sectional comparative study, conducted in pulmonology department of Lahore general hospital from 2016-2017 using convenient sampling technique. The research has been carried out according to the Helsinki declaration of human rights. Research synopsis was approved from the ethical committee of Postgraduate Medical Institute Lahore (PGMI).

Non obese male subjects in the age range of 50 - 70 years were taken. n=23 was selected for each group derived from frequency domain[14]. 3 groups were included in study. Group I

Included Healthy non-smokers. Group II and group III included ex cigarette smokers (at least 10 pack years) and currently nonsmokers foratleast one year [15].In Group II, subjects taken were Grade I and II patients of COPD according to GOLD staging.In GroupIII , subjects recruited were Grade III patients of COPD according to GOLD staging.

Clinically stable (free of exacerbation for a least last 1 month), ambulatory patients of COPD were part of this study.

Subjects with hypertension, diabetes mellitus, exacerbating patients of COPD, stage IV patients of COPD were excluded. Those who took any medication affecting ANS (beta blockers, anticholinergic, anxiolytics) within 6 hours of testing and subjects with panic attacks were also excluded.

Informed consents were taken .History and examination were performed.The participants were instructed not to take a large meal, drink tea or coffee 2-3 hours before test[16] and to abstain from strenuous exercise 24 hours before the test[17]. HRV and Pulmonary function tests were conducted between 8am to 11am due to diurnal changes in both the parameters.Room temperature was kept between 23±2°C and humidity at 40 to 60%[18].

An expert spirometry technician and a pulmonologist supervised the testing.Subjects were given time to relaxebefore and during the tests.

To record pulmonary function tests FVC maneuver was done. The subjects were asked to inspire maximally, exhale with force and to continue complete exhalation to the end of test (EOT). During test subjects were instructed to seal lips around mouthpiece and nose clips were applied. It was taken into care that the inspiration was fast. Three recording were done and best of the three spirograms was used.

Later to check for reversibility subject was given a bronchodilator (salbutamol) via metered dose inhaler and the test was again repeated after 15 minutes[19].

To record HRV the subjects were briefed to be at rest in supine position with uncrossed legs for approximately 10 minutes. RSA – M (Respiratory Sinus Arrhythmia Maneuver) in supine position was done .For 1 minute heart rate was measured at rest with spontaneous breathingLater for 4 minutes heart rate was recorded while performing actual RSA – M. During RSA-M subjects were explained to perform series of slow and deep inhalation and exhalation. Each respiratory cycle during RSAM was of 10 seconds i.e., 5 seconds for exhalation and 5 seconds for inhalation, corresponding to six cycles of deep breathing per minute. To end with the test, For 1 minute heart rate was recorded at rest with spontaneous breathing[20].HRV was then assessed in frequency domain using

KUBIOS HRV 3.3.0 STANDARD software[21].

Data was assessed using IBM SPSS Version 23. Normality of data was checked by Shapiro Wilk test. Median (IQR) were calculated. Kruskal Wallis test and Mann Whitney U test were applied. *P* value < 0.05 was considered statistically significant

RESULTS

Low Frequency (LF) which reflects sympathetic activity in frequency domain was lower in patients of COPD as compared to controls (*p* value < 0.001) (Table 1) . High Frequency (HF) was significantly lower in patients of COPD as compared to controls (*p*value< 0.05) (Table 1).Median IQR for LF (ms²) showed further significant decrease (*p* value<0.001) as disease progressed (Group II: 226(155) and Group III:100(23)) (Table 3) Median IQR for HF (ms²) comparing COPD patients in 2 groups, (Group II: 338(185) and Group III: 360(211)) was significantly increased with advancement of disease (***p*** value < 0.05) (Table 3). LF/HF ratio which calculates the sympathovagal balance, given in Median (IQR) among the three study groups reflected a significantly lowered sympathovagal balance in patients of COPD (***p*** value <0.001) (Table 1).

Table 1: Comparison of parameters of Heart Rate Variability (HRV) in frequency domain among study groups using Kruskal Wallis Test

Variable	Group I (n=23)	Group II (n=23)	Group III (n=23)	*p* value
LF (ms²)	465(415)	226(155)	100(23)	< 0.001*
HF (ms²)	456(245)	338(185)	360(211)	0.004*
LF/HF	1.2(0.44)	0.6(0.65)	0.33(0.26)	< 0.001*

***p* value significant

Table 2: Comparison of parameters of HRV in frequency domain between Group I and Group II using Mann Whitney U test

Variable	Group I (n=23)	Group II (n=23)	*p* value
LF (ms²)	465(415)	226(155)	<0.001*
HF (ms²)	456(245)	338(185)	0.004*
LF/HF	1.2(0.44)	0.6(0.65)	<0.001*

***p* value significant

Table 3: Comparison of parameters of HRV in frequency domain between Group II and Group III using Mann Whitney U test

Variable	Group II (n=23)	Group III (n=23)	*p* value
LF (ms²)	226(155)	100(23)	0.004*
HF (ms²)	338(185)	360(211)	0.004*
LF/HF	0.6(0.65)	0.33(0.26)	0.006*

***p* value significant

Table 4: Comparison of parameters of HRV in frequency domain between Group I and Group III using Mann Whitney U test

Variable	Group I (n=23)	Group III (n=23)	*p* value
LF (ms²)	465(415)	100(23)	<0.001*
HF (ms²)	456(245)	360(211)	0.006*
LF/HF	1.2(0.44)	0.33(0.26)	<0.001*

***p* value significant

DISCUSSION

The HRV is a noninvasive method, largely used to quantify functioning of the ANS. It shows changes in R-R intervals In the present study, age and BMI matched healthy and COPD male subjects were included in 3 groups (n=23 each). Group I included healthy subjects whereas Group II consisted of mild + moderate stage and Group III recruited severe stage COPD patients. This study was conducted to assess and compare HRV in frequency domain in COPD patients with healthy subjecs.

Comparing all 3 study group LF, HF and LF/HF ratio were all significantly lower in COPD patients as compared to healthy controls (***p*** value < 0.05).

These results indicate a reduced sympathovagal balance, a lower sympathetic and parasympathetic modulation in COPD patients as compared to healthy controls.

The present study also compared Group II with Group III for link between HRV and disease progression in COPD. LF and LF/HF ratio were significantly reduced in Group III as compared to Group II (*p* value < 0.05). HF however was significantly raised in Group III as compared to Group II (*p* value < 0.05). These results indicate that with advancement of disease, sympathetic modulation and sympathovagal balance were lowered as explained by lower LF and LF/HF ratio respectively. However vagal activity was enhanced in later stages of COPD as shown by higher HF values. In line with these results previous studies have indicated that there is significant reduction in several parameters of HRV both in frequency domain. A study by [20] have reported a reduction in parameters of HRV in frequency domain (LF and HF) indicating both a reduced SNS and PSNS modulation in COPD patients as compared to controls. They have demonstrated that cardiac autonomic control of heart rate was linked with inspiratory muscle weakness in COPD. [22] recorded 24 hour ECG of clinically stable COPD patients and healthy controls. Diseased subjects showed a diminished LF/HF ratio during the entire recording. Their results suggest a reduced sympathovagal balance in patients of COPD as compared to healthy subjects.

A few studies have reported results in opposition to the present study[23]; conducted a study on COPD patients to measure HRV parameters (HF and LF). In their results LF was significantly greater in COPD patients. However they had patients with hypoxemia, which itself is a factor to alter sympathetic modulation. [24] conducted a study on COPD patients of all stages of disease severity according to GOLD guidelines. FVC maneuver was conducted while monitoring Heart Rate during the maneuver. HRV measured in frequency domain (LF, HF and LF/HF), did not show any significant differences between the diseased and control group. This may be linked to increased age of the subjects (72±7 years).

Comparing diseased groups of COPD patients with each other, in line with present study, [25]measured HRV using Holter monitor. LF and LF/HF ratio decreased with increasing severity of COPD. It reflects a depressed sympathovagal balance and SNS activity. [26] conducted a study on COPD patients during spontaneous breathing and BIPAP ventilation. They found HF to be higher in spontaneous breathing, referring to this increase in HF due increased PSNS activity that leads to reduced FEV1 and bronchoconstriction usually seen in patients of COPD.

Contrary to present study, [27] conducted a literature review over increased SNS activity in COPD patients. They attributed this finding in COPD to enhanced oxidative stress, a catecholamines spillover from activated sympathetic nerve fibers and impaired baroreceptors sensitivity in COPD .

CONCLUSION

In the present study it is concluded thatall parameters of HRV studied were low in frequency domain .Advancement of disease caused a reduction in sympathovagal balance and sympathetic activity indicated by decreased values variables of HRV that were assessed. HF from frequency domain however was higher in patients with advanced disease, indicating a probable enhancement in vagal modulation as disease deteriorates.

Limitations and recommendations: This study did not include female COPD patients, they must also have been a part of study to minimize any gender bias while measuring autonomic imbalance in patients of COPD.

COPD according to WHO has a greater mortality ratio in developing countries. So, in light of present study, measurement of HRV can help in earlier

detection and management of cardiac issues such as arrhythmias in COPD.

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