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IMPACT OF COVID-19 ON HEART RATEVARIABILITY AND PULMONARY FUNCTION TESTS PARAMETERSAMONG PATIENTS WITH CHRONIC LUNG DISEASES - A CROSS SECTIONAL STUDY

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Abstract

Introduction : *Covid 19 pandemic, a contagious disease caused by virus, SARS- Cov-2 affected many systems in human body, predominantly respiratory and cardiovascular system.But these effects on the autonomicnervous system (ANS) in different locations in the world, over the long term remain unclear. Therefore, we tried to evaluate the alterations in cardiac autonomic functioning with long-term manifestations in population with chronic lung diseases of South India. Impaired lung compliance may have changes in pulmonary function tests (PFT) in chronic lung diseases along with variations in heart rate variability (HRV). HRV gives information about sympathovagal autonomic drives and used as a tool for the assessment of autonomic imbalance. Analysis of the beat to beat variation of cardiac R-R intervals has been used to quantify alteration in cardiac autonomic regulation.*

Aim: *To study the association of Covid – 19 with HRV and PFT among patients with chronic lung diseases.*

Materials and methods: *A cross sectional study was conducted in patients with interstitial lung diseases (ILD) and chronic obstructive pulmonary diseases (COPD) who had contracted with covid -19 and compared with control group of non covid ILD and COPD patients. Spectral analysis of HRV and PFT were taken in both groups and compared the changes. A total of 90 ILD and 125 COPD patients of age group 55-65 years were studied and compared with age and sex matched control group.*

Results: *The difference of PFT and HRV in both groups were analyzed by unpaired 'T' test and the difference of categorical variable in both groups wereanalyzed by Chisquare test.*

All the covid patients, showed an increase in sympathetic activity irrespective of gender. Low Frequency and High Frequency Ratio (LF:HF ratio) was significantly more in females with Covid 19 compared to that of males. FEV1 % pred. was less in both the gender but females showed better values (73%).

Conclusion: *There were significant changes in Lfnu, HFnu and LF/HF ratio ($p \leq 0.001$), FEV1 % pred., FEV1/ FVC ratio predicted and PEF among both COPD and ILD patients when compared with Covid infected patients and shows that there increase in sympathetic tone with Covid infection.*

Key words: *Covid - 19, heart rate variability, LF/HF ratio, chronic lung diseases, ILD, COPD, pulmonary function test, autonomic imbalance*

INTRODUCTION

The COVID-19 caused bya new corona virus (SARS-CoV-2) which was emerged in Wuhan,China, became a pandemic in March 2020. This created morbidity and high mortality rate worldwide (3.4%) and comparatively less in India (1.2%) and Kerala (<1%). COVID-19 showedasymptomatic and symptomatic features and the clinical manifestations of symptoms were fever, headache, myalgia, sore throat,cough, anosmia and in severe cases viral pneumonia as well as hypoxia (low SpO2). This disease targeted on various tissues like lung parenchyma, myocardium, hypothalamus, pituitary, etc.[1,2]. Many patients continue to experience chronic post covid symptoms such as heart palpitations, fatigue, orthostatic intolerance, dizziness, brain fog,anxietyand syncope[3]. Those with chronic lung diseases were more affected and showed difficulty in respiratory as well as cardiovascular functions. Obstructive Lung Diseases (OLD) are associated with constricted airways with increased airway resistance as in the case of Chronic Obstructive Pulmonary Disease (COPD), Asthma, Bronchiectasis, etc[4]. Some studies reported the association betweenhigh mortality rate and pre-existing COPD [5]. Interstitial lung disease (ILD) is a group of restrictive disorders that cause scarring (fibrosis) of the lungs which makes it difficult to breathe. Some studies during the time of COVID -19 demonstrated that patients with ILD were more likely to haveseverity in COVID symptoms compared with those without. It was also indicated that ILD patients were prone to infection easily [6].

Chronic lung diseases are usually accompanied by cardiovascular comorbidities too. Autonomic nervous system (ANS)is important in the regulation of cardiovascular system. Dysfunction of autonomic nervous system is caused by the failure of sympathetic and parasympathetic components of it. Analysis of the beat to beat variability of cardiac R-R intervals has been used to quantify alteration in cardiac autonomic regulation by the help of HRV analysis [7,9]. This analysis has time domain as well as frequency domain components and can be performed on short (upto 5 min) or long 2(4 hours) ECG recordings. Diminished HRV can occur in a broad range of critical illnesses especially with cardiovascular diseases[8].

As mentioned above, these studies propose that there is relation with alterations in HRV in chronic lung disease patients with the manifestation of COVID-19. Pulmonary Function Tests (PFT) is useful in distinguishing between restrictive and obstructive lung diseases. FEV_1 is reproducible and is highly sensitive index of obstructive lung disorder. Alterations in the PFT are accompanied by changes in HRV in many respiratory diseases. There are studies which correlates the association of PFT in both ILD and COPD patients and PFT is used as a clinical tool for the prognosis of these diseases. Though some studies mention about the cardiovascular comorbidities with respiratory diseases in COVID -19 patients, the autonomic imbalance is not investigated well, especially with ILD. Patients with COVID-19 with low HRV areindicated for intensive care unit admission in the first weekafter hospitalization, regardless of age and chronic heart diseasestatus [10]. Understanding the relationship of HRV / PFT in chronic lung diseases may help us to find out whether HRV can also be used as a clinical tool in the assessment and management of chronic lung diseases other than PFT.The primary objective of this study is to investigate the autonomic changes along with PFT among COVID-19 patients with chronic lung diseases.

MATERIALS AND METHODS:

A cross-sectional study was conducted at the Department of Pulmonary medicine and Physiology, in a tertiary care hospital in Kerala, India, on patients with chronic lung diseases. The study was conducted after lock down of Covid-19. The participants were well informed about the study and written consent was obtained from them. The protocol was presented to the Institutional Ethics Committee (IEC), and approval was obtained (Ref No:10/IEC/20/AIMS-29).

Inclusion criteria

Patients with ILD and COPD who were screened for COVID-19through RTPCR/Antigen test, were included in the study.There were a total of 215 consecutive patients and 90 were with restrictive lung disease (ILD) and 125 were with COPD. The COVID-19 study group were with mild to moderate symptoms with SPO_2 90% in room air and rest of the age and sex matched ILD and COPD patients without COVID -19 were taken as the control group.

Exclusion criteria

Patients with uncontrolled systemic arterial hypertension and uncontrolled pulmonary hypertension, pulmonary embolism, giddiness on standing, syncopal spells, any disease or conditions affecting autonomic functions like polio, tuberculosis, nerve degenerative disorders, Congestive heart failure, Ischemic heart disease, valvular heart disease, conduction disorders, patients receiving drugs that can interfere with cardiac function eg: beta blockers were excluded from the study.

Sample size

From the study conducted by R. E. Kleiger et al. (7), the sample size is calculated as n = 43 in both ILD and COPD groups.

The study participants were with chronic lung diseases and divided into COPD and ILD with and without COVID. All the patients with COVID-19 syndrome had the symptoms 4-6 months backwith mild to moderate difficulties(people with mild symptoms of COVID-19 were symptomatic but didnot have complications of severe hypoxia and major viral pneumonia; people with moderate cases had clinical signs of pneumonia but did not have signs of complications, such asSPO2 90% in room air). All patients were symptomatic for 8-12 weeks with fatigue,dizziness, inappropriate palpitations, orthostatic intolerance,brain fog, nausea, anxietyand syncope. Moderately symptomatic patients were hospitalized during this period.All cases of COVID-19were confirmed through real-time reverse-transcriptasepolymerase chain reaction assays on nasopharyngeal swabs.None of the patients were with active COVID-19 disease symptoms during this evaluation (asymptomatic for atleast 1 month).

Patients were categorized into COPD and ILD groups based on the GOLD criteria of spirometry, clinical history with questionnaire,comorbidities, 6 MWT, high resolution computed tomography scan (HRCT)and routine blood investigations. Spirometry was done using Spirotrac - Software Reference Number: 68606 V1.16 Vitalograph. All patients with abaseline SpO2 ≥90% weretaken up for the 6 MWT in a 100 m long passage near the out patient clinic.

Assessment of HRV: All the study participants were instructed to avoid consuming caffeine derivativesat least 24 h prior to the test. Before the recording, the volunteers were given rest for 15min, and HRV was recorded in supine position for 10min. The patients were instructed to be relaxed with eyes closed, without sleeping, talking and moving, to prevent interference during the test. The lab temperature was maintained between 22°C and 24°C using air conditioner. The Heart Rate (HR) was recorded using Physiopac PC -2004 versionthat captured the R wave on theelectrocardiogram. Thedistance between two consecutive peaks of the R wave is considered as the RR interval (the fluctuations in the intervals betweenconsecutive heartbeats).

HRV was analyzed by Frequency domain analysis. Frequency domain analysisutilized the fast Fourier transform (FFT) of the time series. The application of this algorithm permitted the identification of the power spectral density (PSD) as well as its frequency bands: very low frequency (VLF), low frequency (LF), and high frequency (HF). Two frequency bands that best represent the vagal and sympathetic activity of HR control were used in this study. Signals in the LF band (0.04 to 0.15 Hz) have been predominately attributed to high sympathetic tone and low parasympathetic tone. On the other hand, signals in the HF band (0.15 to 0.4) have been attributed only to parasympathetic activity.Spectral components were obtained in both absolute (ms2) and normalized units (nu) [11]. The data collected during the first 30 s and final 30 swere discarded.

STATISTICAL ANALYSIS

The data was entered in to Excel worksheet and analysis performed using SPSS 23. Descriptive and inferential statistical analysis were carried out. Results on quantitative measurements are presented on mean} SD and results on categorical measurements are presented in number (%). Significance is assessed at 5% level. Normality of data was tested using Shapiro wilk test. The difference of PFT and HRV in both groups was analyzed by students ‘T’ test (unpaired t test) and the Mann Whitney test. The difference of categorical variable in both groups were analyzed by Chisquare test. The relation between PFT and HRV was analyzed by linear regression.

RESULTS

This cross sectional study was done at a tertiary care hospital in Kerala and a total of 215 consecutive patients participated with the written consent and there were 90 restrictive lung disease (ILD) and 125 COPD patients.Female patients were little higher in ILD group compared to COPD. Most common comorbidities in both groups were diabetes (31% in COPD, 28 % in ILD). Both the study groups were further divided into those with and without COVID -19 infection and all the parameters were analyzed among all these groups. The difference of PFT and HRV in both groups was analyzed by students 'T' test (unpaired t test).

Age and duration of the disease among both COPD and ILD groups showed significance in the demographic variables. The basal recordings of systolic and diastolic pressure were taken.[Table-1].

[Table-1]: Demographic features of COPD (N= 125: Non Covid - 61 and Covid - 64) and ILD patients (N= 90: Non Covid - 40 and Covid - 50

Demographic variables	Group	Mean±sd	P value (Unpaired t test)	Mean±sd	P value (Unpaired t test)
Category		**COPD**		**ILD**	
Age (in years)	Non covid	61.89±1.624	0.8002	61.45±1.084	0.2808
	Covid	61.95±1.361		60.98±2.559	
BMI ($kg/m^{2)}$	Non covid	23.56±4.315	0.067	25.25±5.34	0.345
	Covid	24.60±1.889		26.18±4.43	
Duration of the disease (in years)	Non covid	3.83±.72	0.3171	4.04±0.807	0.2043
	Covid	3.705±0.64		3.825±0.78	
Systolic Blood Pressure (mmHg)	Non covid	129.97±6.971	0.831	127.41±8.32	0.275
	Covid	129.61±11.347		123.31±23.63	
Diastolic Blood Pressure (mmHg)	Non covid	78.82±13.314	0.268	80.32±3.39	0.959
	Covid	80.78±6.222		80.36±4.99	

In the COPD group, spectral analysis of HRV with all its components like LFnu, HFnu and LF/HF ratio showed high significant result ($p \leq 0.0001$). In ILD group, all the HRV components like LF/HF ratio, LFnu ($p \leq 0.0001$) and HFnu ($p \leq 0.002$) showed high significant result [Table-2].

[Table-2]: HRV parameters of COPD patients (N =125), ILD patients (N=90)

Parameters	Group	Mean	P value	Mean	P value
Category		**COPD**		**ILD**	
LF/HF ratio	Non covid	1.125±0.46	0.0001	1.93±0.99	0.0001
	Covid	3.083±1.325		3.89±1.86	
LFnu	Non covid	48.97±8.66	0.0001	63.98±13.37	0.0001
	Covid	71.35±7.622		78.04±8.55	
HFnu	Non covid	48.93±10.986	0.0001	33.98±11.15	0.002
	Covid	28.18±11.637		26.58±11.50	

In COPD patients, FEV1 % predicted and FEV1/FVC % predicted were significant compared to other PFT parameters whereas major PFT parameters in both groups were similar and not significant except for FEV1 % predicted and PEF values[Table-3].

[Table-3]: PFT parameters of COPD patients (N =125), ILD patients (N=90)

Parameters	Group	Mean	P value	Mean	P value
Category		**COPD**		**ILD**	
Resp Rate	Non covid	22.26±5.721	0.0368	20.64±2.72	0.028
	Covid	20.370±4.21		19.42±2.67	
FVC (% predicted)	Non covid	66.64±17.574	0.616	68.57±19.24	0.299
	Covid	65.19±15.569		74.24±21.61	
FEV1 (% predicted)	Non covid	55.00±24.534	0.0482	64.09±15.05	0.045
	Covid	58.47±20.368		70.85±16.97	
FEV1/ FVC (%)	Non covid	82.72±19.819	0.023	104.82±10.38	0.628
	Covid	90.13±17.418		106.05±14.10	
PEF (L/min)	Non covid	242.52±96.171	0.363	256.14±102.84	0.019
	Covid	257.68±94.260		311.51±123.04	

The mean of 6MWT distance, HR and SPO_2values before and after the walk test in non COVID group and COVID group in COPD as well as ILD patients were found significant. The mean oxygen saturation before 6MWT also showed significant results. [Table-4].

[Table-4]: SPO_2 – Oxygen saturation, 6MWT – 6 minute walk test in COPD patients (N =125), ILD patients (N=90)

Parameters	Group	Mean	P value	Mean	P value
Category		**COPD**		**ILD**	
Basal HR (before 6MWT)	Non covid	242.52±96.171	0.363	256.14±102.84	0.019
	Covid	257.68±94.260		311.51±123.04	
Basal SPO_2(before 6MWT)	Non covid	82.21±10.569	0.913	88.57±12	0.518
	Covid	90.04±21.930		90.31±14.17	
6MWT (Meters covered)	Non covid	96.66±2.323	0.042	93.55±2.56	0.0471
	Covid	95.86±5.147		96.85±2.77	
HR (after 6MWT)	Non covid	419.67±84.300	0.001	95.47±5.19	0.005
	Covid	364.58±93.894		103.76±18.36	
SPO_2(after 6MWT)	Non covid	97.30±9.82	0.035	93.27±2.46	0.021
	Covid	90.43±7.44		88.33±5.16	

Various age groups among COPD patients were categorized on the basis of Covid infection using fisher exact test and found significant [Table-5]. But the gender wise analysis of HRV and PFT parameters didn't give much difference and were insignificant.

[Table 5]: Difference in contract of Covid infection in various age groups among COPD patients.

Age	Groups		Total	P value (fisher exact test)
	Non Covid	Covid		
51-55	3	0	3	0.001
56-60	16	7	23	
61-65	39	42	81	
66-70	3	15	15	
Total	61	64	125	

The data was analyzed to compare among males and females. Out of 90 ILD patients, 45% were males with Covid and 49% were males without Covid and females were comparatively more. Male predominance was seen in COPD patients with Covid (55%) whereas non Covid patients were found almost equal. LF/HF ratio was very high in female Covid patients among ILD when compared to COPD. FEV1 % value was better in female Covid patients in both the groups though it is less.However no parameters were found significant

[Table-6].

[Table-6]: HRV and PFT parameters among males and females of ILD and COPD patients with Covid infection.

Parameters	Sex	ILD patients (N=50)			COPD patients (N=64)		
		Covid (N)	Mean±sd	P value (Unpaired t test)	Covid (N)	Mean	P value (Unpaired t test)
LF/HF	M	23	3.76±1.05	0.639	34	3.15±1.76	0.642
	F	27	4.00±2.34		30	2.98±0.96	
Lfnu	M	23	78.72±8.04	0.593	34	71.80±6.11	0.577
	F	27	77.47±9.05		30	70.78±9.24	
Hfnu	M	23	27.28±11.75	0.689	34	29.60±14.30	0.250
	F	27	26.00±11.45		30	26.41±6.84	
FVC	M	23	68.84±12.65	0.075	34	64.45±17.73	0.653
	F	27	78.73±26.28		30	66.13±12.56	
FEV1 %	M	23	68.84±15.53	0.420	34	55.85±21.30	0.224
	F	27	72.53±18.17		30	61.75±18.95	
FEV1/ FVC ratio % predicted	M	23	105.64±17.79	0.85	34	86.95±17.61	0.082
	F	27	106.40±10.40		30	94.09±16.58	
PEF L/min	M	23	321.16±127.55	0.602	34	240.45±79.15	0.095
	F	27	303.47±12.75		30	279.22±107.72	
HR - end	M	23	105.12±24.55	0.622	34	94.20±27.23	0.072
	F	27	102.63±11.23		30	84.84±10.88	
SPO2 - end	M	23	94.44±5	0.147	34	95.40±6.61	0.399
	F	27	92.40±5.203		30	96.44±2.24	

Though many parameters didn't show significant change when compared with Covid and non Covid group, most of them showed significant result when compared with COPD and ILD groups with Covid [Table/Fig-7].

[Table-7]: Comparison of HRV and PFT parameters in COPD(64) and ILD (50) patients with Covid.

Parameters	Covid Group	Mean±sd	P value (Un paired t test)
LFnu	ILD	78.04±8.557	0.001
	COPD	71.15±7.753	
HFnu	ILD	26.58±11.500	0.380
	COPD	28.41±11.722	
LF/HF ratio	ILD	3.89±1.86	0.005
	COPD	3.061±1.452	
FEV1 (% predicted)	ILD	70.85±16.975	0.001
	COPD	58.82±20.446	
FEV1/ FVC ratio (%)	ILD	106.05±14.106	0.001
	COPD	90.27±17.343	
FVC (% predicted)	ILD	74.24±21.610	0.009
	COPD	65.47±15.633	
PEF L/min	ILD	311.51±123.048	0.008
	COPD	259.36±94.692	

DISCUSSION

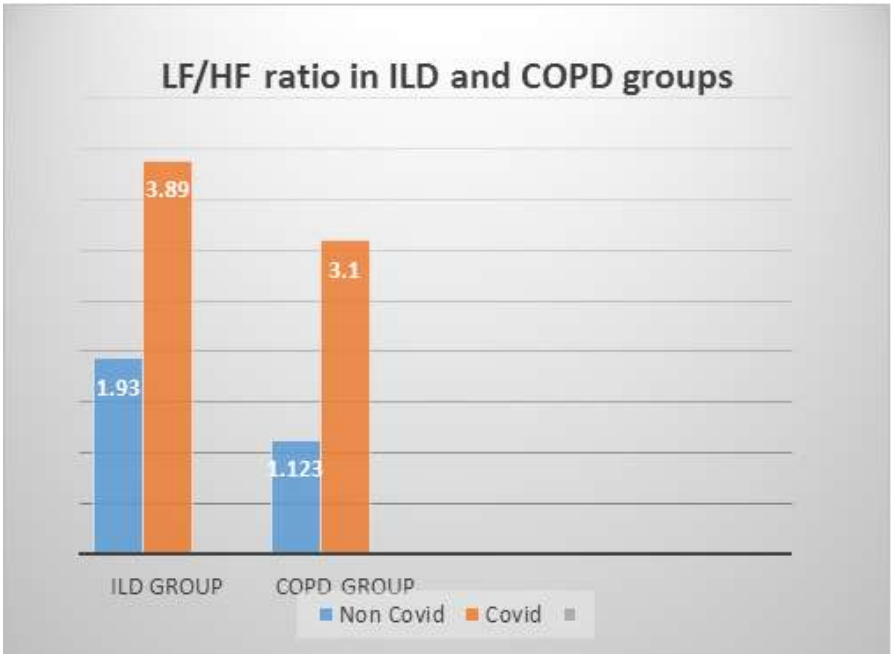
Covid-19 has been a severe threat for many people especially with chronic lung diseases. People with coronary artery diseases (CAD) seem to have further complications with the same. The present study showed that there are obvious changes in heart rate variability as well as pulmonary function tests with Covid-19 among people with chronic lung diseases. Some of the parameters were abnormal in the control group too which included patients with chronic lung diseases and without Covid.

Obstructive and restrictive type of lung diseases were studied and HRV variables showed high significance in these disease groups. COPD is a heterogeneous clinical syndrome characterized by chronic airway obstruction with increased airway resistance and is frequently associated with cardiovascular diseases. Restrictive Lung Disease (RLD) is characterized by impaired compliance. A reduction in lung volume is associated with restrictive diseases like Sarcoidosis, Tuberculosis, fibrosis, scoliosis, kyphosis, pleural effusion, etc.

The diagnosis and assessment of lung diseases are done mainly by the Pulmonary function tests, FEV1 being the reliable marker according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2018(4). There are studies conducted to show prevalence of type of respiratory diseases. Antwi et al. studied using the data of PFT of 762 patients and concluded that obstructive respiratory diseases are most prevalent among the subjects[12]. In the current study also, obstructive diseases were more compared to restrictive. HRV is a simple and noninvasive measure of autonomic impulses and it can be done both in time and frequency domain parameters. Chhabra et al. conducted a study on sixty three stable patients of COPD and 36 controls who underwent spirometry, estimation of diffusion capacity, 6-minute walk test (6MWT) and measurements of serum interleukin-6 (IL-6) and high-sensitivity C-Reactive protein. Their reports say that patients with COPD have increased cardiac autonomic modulation with sympathetic dominance. This is associated with decreased lung diffusion capacity and systemic inflammation. Modification of cardiac autonomic dysfunction may therefore be of benefit in the treatment of COPD patient[13]. There are studies which shows that there is parasympathetic dominance in post Covid male subjects with mild symptoms in comparison to the control group who did not have COVID-19 [14].

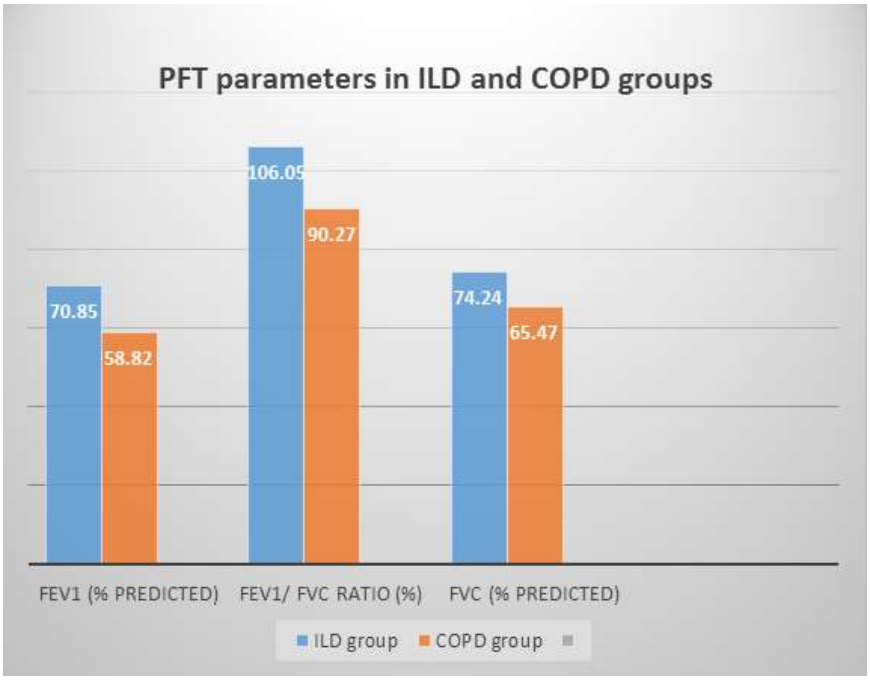
Lung damage from many ILDs is irreversible and progressive. Some example of ILDs include, Idiopathic Pulmonary Fibrosis, Hypersensitivity Pneumonitis, Sarcoidosis, Asbestosis, Cystic fibrosis. In a study related to HRV indices in 18 children with cystic fibrosis by Melitta et al. the findings support the utilisation of time and relative frequency domain HRV indices as a prognostic tool in children with CF [15].The study done by Aline Fernanda et al. was to analyze heart rate dynamics in subjects with chronic COPD by measures of heart rate variability. 38 adults were divided into two equal groups based on respiratory function: COPD and normal. They found that HRV analysis can be a Clinical and Diagnostic Tool in COPD and can be helpful in treatment [16].

In this study, it is clear that all the HRV variables in Covid group are significant when compared to the non Covid group. The normalized units of LF and HF represents the increased sympathetic drive and vagal drive respectively. These parameters were high in Covid groups and indicates that there is increase in sympathetic drive which is an autonomic dysfunction. LF/HF ratio less than 1 indicates good cardiovascular health and in this study it was very high in all the groups. Thus it proves that there is increased sympathetic activity with decreased total power. This is implicated with adverse cardiovascular morbidities and mortalities. There are studies to support the evidence of increased sympathetic tone in long Covid patients [17] But some studies shows that there is parasympathetic dominance in post Covid patients [18,19]. Much before the onset of clinical symptoms of cardiovascular diseases, these alterations can be observed and especially with the manifestation of Covid, the chances for cardiovasular diseases are high. It is also clear that all these HRV parameters are highly increased in Covid groups of ILD than the COPD [Fig-1]. This shows that those with ILD are more prone to cardiovascular diseases. In some studies it appears that patients with ILD are indeed more susceptible to contracting COVID-19. Following COVID-19 pneumonia, several groups have described persistentparenchymal abnormalities which have been described as post-Covid ILD in general [6].



[Fig-1]: Comparison of LF/HF ratio in ILD and COPD patients with Non Covid and Covid subgroups with p value 0.001.

Among the PFT parameters, not much significant change observed in none of the groups in this current study. Though there was reduction in lung capacities like FEV1% predicted, FVC % predicted, FEV1/FVC % and PEFR, better results were observed in ILD group [Fig-2]. Distance covered by the Covid group in both ILD and COPD were less when observed 6MWT. Also it showed that the basal HR was more and basal SPO_2 was less among those with Covid. This further supports the sympathetic predominance in Covid group.



[Fig-2]: Comparison of FEV1% predicted, FEV1/FVC %, FVC % predicted, in ILD and COPD patients with Covid subgroups with p value 0.001.

CONCLUSION

Our study demonstrates that there is significant increase in sympathetic tone by the analysis of frequency domain HRV assessment irrespective of obstructive or restrictive lung disease patients and especially with Covid manifestation. It was noted that pulmonary function tests results are better with ILD patients though there is an expected decrease in these diseased groups. The 6MWT distance, HR and $SPO_2$and mean oxygen saturation values before and after the walk test in COPD as well as ILD patients were significant when compared among COVID and no COVID patients. In general the ILD group is more prone to get affected with cardiovascular diseases with the involvement of Covid-19. It is suggested to include HRV also as a clinical tool in the early diagnosis and management of these lung diseases apart from PFT.

LIMITATIONS

This was a single center study and the study participants including the control groups were already chronic lung disease patients. The interference of medication was not considered and evaluated during the assessment. Could not do follow up of these patients and therefore the reliability of these results in long term assessment has to be studied further.

ETHICAL CONSIDERATIONS

☐ Approval from the Institutional Research committee and ethical committee was obtained for the study.

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CONFLICT OF INTEREST

There is no conflict of interests regarding this study.

FINANCIAL DISCLOSURE - Nil

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