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Research Article

Evolution of ECG Abnormalities in Immune Dysfunction Exacerbation Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is a major cause of death worldwide. Early identification of the complications, particularly, atherosclerosis, pulmonary hypertension and right ventricular dysfunction can prevent or delay long-term complications. The aim of the present study was to evaluate the prevalence of ECG abnormalities in COPD patients with exacerbation and COPD phenotypes.

Methods: The study population consisted of 364 COPD patients aged 21 to 85 years of either sex. This study was carried out in the department of pulmonology, Osh Interregional United Clinical Hospital, Osh, Kyrgyzstan. Between December 2016 to February 2020. The patients who are diagnosed as having COPD as per GOLD guidelines. ECG was performed with the help of Department of Cardiology.

Results: Highest cases of COPD were found in the age group of 51-65. According to physical examination, spirometry and x-ray out of 364 COPD patients, blue bloaters (BB) 257 (70.60%), Pink puffers (PP) 41 (11.26%) and Mixed 66 (18.31%) were found. Highest BB and mixed were found in 51-65 age group, PP in > 65 age group. Out of 218 male COPD patients, BB 149 (66.97%), PP 26 (11.93%) and Mixed 43 (19.72%) were found. Out of 146 female COPD patients, BB 108 (73.97%), PP 15 (10.27%) and Mixed 23 (15.75%) were found.

Out of 364 patients P wave was abnormal in 128 (35.16%). Tachycardia was observed in 113 (31.04%), Bradycardia 9 (2.47%) and 247 (66.86%) were with normal heart rate. Right heart axis deviation was found in 77 (21.15%), left 39 (10.17%), vertical 1 (0.27%) and 247 (66.86%) found normal. Vertical heart positioned patients found 87 (23.90%), horizontal 38 (10.44%) and 239 (65.66%) found normal. Low voltage was observed in 20 (5.49%). Incomplete right bundle branch block found in 64 (17.58%) and complete right bundle branch block found in 02 (0.55%). ST changes observed in 146 (40.11%). Tall RV1 was seen in 42 (11.54%) and Deep SV6 was observed in 169 (46.43%).

Conclusion: Comparative prevalence was higher in males and 51 - 65 age group at high risk in both sex. Highest BB and mixed found in 51 - 65 age group, PP in > 65 age group. Phenotype BB was more prevalent.ECG abnormalities P-pulmonale, Tachycardia, Right heart axis deviation, Vertical heart position, IRBBB, ST changes Tall RV1 and SV6 was most prevalent. Early diagnosis and management can prevent disease progression of atherosclerosis and hypertension.

Keywords: COPD; Electrocardiography; Blue Bloaters; Pink Puffers; Hypertension; Atherosclerosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease caused by an anomalous activation of the immune system because of lung exposure to irritants affecting normal breathing in a progressive manner [1,2]. COPD creates difficulty in proper pulmonary functioning, and this limitation is the main cause for the diagnosis of COPD. Airflow limitation is the slowing of expiratory airflow and it can be measured by Spirometry, which demonstrates a persistently low forced expiratory volume in one second (FEV1) and a low FEV1/forced vital capacity (FVC) ratio even in the presence of treatment [1,2]. Other previously existing disease conditions, which can present together or independently, are the usual leading causes of COPD such as chronic bronchitis, small airway disease.

COPD presents a high prevalence and about 200 million peoples all over the world present the disease, posing COPD as the leading cause of morbidity and mortality among chronic diseases. COPD

is the 4th major cause of death globally and it has been predicted that this disease will become the 3rd one by 2030 [3]. The Global burden of disease project carried out in 2001 identified COPD as the 6th leading cause of death in the developing or underdeveloped world, resulting in 4.9% of total deaths [4]. A recent study identified COPD as the 4th leading cause of chronic morbidity and mortality and reported that the incidence and prevalence of the disease is continuously on the rise [5]. COPD is the reason of many hospital visits and hospitalizations and frequent cause for work absenteeism. In this regard, a patient with COPD causes personal and healthcare system financial burden. It is necessary to diagnose the disease early and identify patients who are likely to develop complications of pulmonary hypertension, right ventricular hypertrophy and cor pulmonale to prevent long-term complications, extending the patient's life while improving health status.

To the best of our knowledge no studies have been done to estimate the prevalence of ECG variabilities and prevalence of Blue bloaters (Chronic bronchitis) and pink puffers (Severe emphysema) in COPD exacerbation patients in osh region of Kyrgyzstan. Therefore, the aim of the present study was to determine the prevalence of ECG abnormalities in patients with COPD exacerbation attending an in and outpatient clinic of Osh Interregional United Clinical Hospital, Kyrgyzstan. In this study, we aimed to see the prevalence of ECG abnormalities and phenotypes of COPD in different sex and age groups.

Material and Method

The study population consisted of 364 COPD patients aged 21 to 85 years of either sex. This study was carried out in the department of pulmonology, Osh Interregional United Clinical Hospital, Osh, Kyrgyzstan. Between December 2016 to February 2020.

The diagnosis of chronic obstructive pulmonary disease is made by symptoms in the history and confirmed by physical examination, radiographic examination and lung spirometry for airway obstruction by Spiroanalyzer.

Methodology

Inclusion criteria

The inclusion criteria of the patients were patients who presented with cough, sputum production, dyspnea (wheeze), confirmed absence of sputum acid fast bacillus (AFB), reduced forced expiratory volume (FEV) (below 80%), FEV < 15% after inhalation of salbutamol bronchodilator, presence of over inflation, ascites, edema, parasternal heave, jugular venous pressure (JVP) elevation, loud P2, or tricuspid murmur, absence of artery dilatation suggestive of pulmonary arterial hypertension or retrosternal space obliteration evaluated by chest X ray. Additionally, presence of p wave morphology in electrocardiogram (ECG), amplitude, 2, +3 +, avF P amplitude > 9 mm, p-axis, R-wave > 5 mm, r/s > 50%, existence of right bundle branch block (RBBB).

Exclusion criteria

Patients with presence of asthma or other chronic restrictive respiratory diseases with need of ventilator, diseases that would potentially stop the study completion, FEV1 > 80% and reversibility test > 15%, or tuberculosis, were excluded from this study.

After recruitment for the study, a thorough physical examination is done and routine investigations were carried out. The patients were subjected to the following examination. The patients who are diagnosed as having chronic obstructive pulmonary disease as per GOLD guidelines with FEV1/FVC [6] (Table 1).

GOLD Stage	Severity	Symptoms	Spirometry
0	At Risk	Chronic cough, sputum production	Normal
I	Mild	With or without Chronic cough or sputum production	FEV1/FVC < 0.70 FEV1 80% predicted
II	Moderate	With or without Chronic cough or sputum production	FEV1/FVC < 0.70 50% ≤ FEV1 < 80% predicted
III	Severe	With or without Chronic cough or sputum production	FEV1/FVC < 0.70 30% ≤ FEV1< 50% predicted
IV	Very Severe	With or without Chronic cough or sputum production	FEV1/FVC < 0.70 FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure

Table 1: Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1 (Based on the guideline of Global initative for Chronic Obstructive Lung Disease (GOLD), 2020).

Electrocardiographic assessment

A standard 12-lead electrocardiography obtained for each using a portable ECG machine. The following criteria are used to detect right ventricular involvement:

1. P-pulmonale pattern (P wave > 2.5 mm) in leads II, III, avF;
2. Right axis deviation of QRS complex;
3. R/S amplitude ratio in V6 is less than 1;
4. R/S amplitude ratio in V1 more than 1;
5. Clockwise rotation of the electrical axis;
6. Right bundle branch block; g. S1, Q3 or S1, S2, S3 patterns.

Thorough echocardiography was performed with the help of Department of Cardiology.

This paper deals with ECG findings among patients of COPD belonging to different age and sex.

Results

Total 364 COPD patients with and without exacerbations were included in this study 59.89% male and 40.10% female (Figure 1).

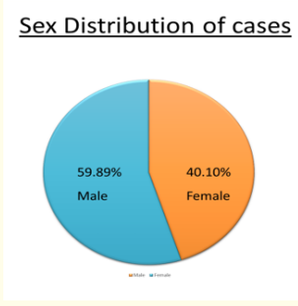

Figure 1

Out of 364 COPD patient 218 were male and 146 females. Highest cases of COPD were found in the age group of 51 - 65 (Table 2).

Age group (in years)	Male	Female	Total
21 - 30	4	7	11 (3.02%)
31 - 40	12	10	22 (6.04%)
41 - 50	20	25	45 (12.36%)
51 - 65	100	64	164 (45.05%)
> 65	82	40	122 (32.97%)
Total	218	146	364

Table 2: Gender distribution of COPD patients.

According to physical examination, spirometry and x-ray out of 364 COPD patients, blue bloaters 257 (70.60%), Pink puffers 41 (11.26%) and Mixed 66 (18.31%) were found. Highest BB found in 51-65 age group, PP in >65 age group, mixed in 51 - 65 age group (Table 3 and Figure 2).

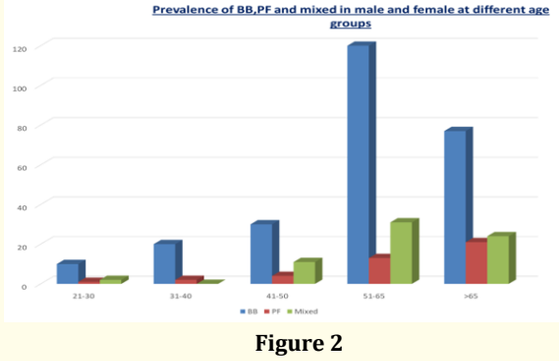

Figure 2

Age group (in years)	BB (%)	PP (%)	Mixed (%)	Total (%)
21 - 30	10	1	0	11
31 - 40	20	2	0	22
41 - 50	30	4	11	45
51 - 65	120	13	31	164
> 65	77	21	24	122
Total	257 (70.60)	41 (11.26)	66 (18.31)	364

Table 3: Prevalence of BB, PP and Mixed in male and female at different age group.

Out of 218 male COPD patients, blue bloaters 146 (66.97%), Pink puffers 26 (11.93%) and Mixed 43 (19.72%) were found. Highest BB found in 51 - 65 age group, PP in > 65 age group, mixed in 51 - 65 age group (Table 4).

Age group (in years)	BB (%)	PP (%)	Mixed (%)	Total (%)
21 - 30	4	0	0	4
31 - 40	11	1	0	12
41 - 50	12	1	7	20
51 - 65	71	9	20	100
> 65	51	15	16	82
Total	149 (66.97)	26 (11.93)	43 (19.72)	218

Table 4: Prevalence of BB, PP and Mixed in Male at different age group.

Out of 146 female COPD patients, blue bloaters 108 (73.97%), Pink puffers 15 (10.27%) and Mixed 23 (15.75%) were found. Highest BB found in 51 - 65 age group, PP in > 65 age group, mixed in 51 - 65 age group (Table 5).

Age group (in years)	BB (%)	PP (%)	Mixed (%)	Total (%)
21 - 30	6	1	0	7
31 - 40	9	1	0	10
41 - 50	18	3	4	25
51 - 65	49	4	11	64
> 65	26	6	8	40
Total	108 (73.97)	15 (10.27)	23 (15.75)	146

Table 5: Prevalence of BB, PP and Mixed in female at different age group.

Out of 364 patients P wave was abnormal in 128 (35.16%). Tachycardia was observed in 113 (31.04%), Bradycardia 9 (2.47%) and 247 (66.86%) were with normal heart rate. Right heart axis deviation was found in 77 (21.15%), left 39 (10.17%), vertical 1 (0.27%) and 247 (66.86%) found normal. Vertical heart positioned patients found 87 (23.90%), horizontal 38 (10.44%) and 239

(65.66%) found normal. Low voltage was observed in 20 (5.49%). Incomplete right bundle branch block found in 64 (17.58%) and complete right bundle branch block found in 02 (0.55%). ST changes observed in 146 (40.11%). Tall RV1 was seen in 42 (11.54%) and Deep SV6 was observed in 169 (46.43%) (Table 6).

S.N.	ECG	Abnormalities	Prevalence (%)
1.	P- Wave	Yes	128 (35.16 %)
		No	236 (65.83%)
2.	Heart rate	Bradycardia < 60	9 (2.47%)
		Normal 60- 100	242 (66.48%)
		Tachycardia > 100	113 (31.04%)
3.	Axis deviation	Right	77 (21.15%)
		Left	39 (10.17%)
		Vertical	01 (0.27%)
		Normal	247 (66.86%)
4.	Heart position	Vertical	87 (23.90%)
		Horizontal	38 (10.44%)
		Normal	239 (65.66%)
5.	Low voltage	Yes	20 (5.49 %)
		No	244 (94.50%)
6.	Bundle Branch Block	IRBBB	64 (17.58%)
		CRBBB	02 (0.55%)
		Normal	298 (81.87%)
7.	ST changes	Yes	146 (40.11%)
		No	218 (59.89%)
8.	Tall RV1	Yes	42 (11.54%)
		No	322 (88.46%)
9.	Deep SV6	Yes	169 (46.43%)
		No	195 (53.57%)

Table 6: Prevalence of ECG Abnormalities in COPD patients.

Out of 364 patients Cough, breathlessness and wheezes was observed in 100% patients. Out of 364 patients rhonchi 75 (20.64%) fever 22 (6.04%) and weight loss 32 (8.79%) was found (Table 7).

S.N.	Symptoms		Prevalence (%)
1.	Cough	Yes	364 (100%)
		No	0 (0%)
2.	Breathlessness	Yes	364 (100%)
		No	0 (0%)
3.	Wheezes	Yes	364 (100%)
		No	0 (0%)
4.	Rhonchi	Yes	75 (20.64%)
		No	289 (79.40%)
5.	Fever	Yes	22 (6.04%)
		No	342 (93.96%)
6.	Weight- Loss	Yes	32 (8.79%)
		No	332 (91.21%)

Table 7: Prevalence of Respiratory and other symptoms in COPD patients.

Discussion

In developing countries, elevated levels of indoor pollution are generated from biomass fuel burning, which has been associated with an increased risk of developing COPD [6]. Many genetic and environmental factors contribute significantly in pathophysiological aspect of COPD. Irritants from cigarette smoke have been reported as the main affecting factor [7]. COPD is triggered when bronchial epithelial cells become damaged because of exposure to air pollution, dust, chemicals, or respiratory infections during childhood, and release of pro-inflammatory mediators to stimulate leukocytes recruitment [6].

When the exposure is chronic in nature, structural and inflammatory cells in the respiratory tract become activated [8,9]. For example, cigarette smoke activates pulmonary innate immune defense mechanism altering the epithelial barrier, stimulating clearance in mucosal tissue, and releasing antimicrobial peptides, complement components, and surfactants. The immune response reduces motility of cilia which affects mucus removal and causes tissue damage.

In patients with COPD, the innate immune mechanism is activated when respiratory infections are sensed via pathogen-associated molecular pattern–pattern recognition receptor and/or damage-associated molecular pattern pathways [10,11]. The receptors stimulation results in activation of alveolar macrophages, monocytes, mast cells, natural killer cells, dendritic cells, neutrophils, and CD8+ T cells. These are the prime cells involved in the immunological changes of COPD [8,9,12]. On the other side, inhaled irritants can activate pro-inflammatory mediators, such as interleukin (IL)-8 (IL8)/CXCL8, IL-1β and tumor necrosis factor-α (TNF-α) [13,14].

Typically, phagocytes control infections but they also control the associated inflammation in healthy subjects; alveolar macrophages phagocytose infiltrated neutrophils and regulate the extent of inflammation by anti-inflammatory processes [15,16]. However, patients with COPD present a reduced self-limitation of inflammation by macrophages which, in addition to the induction of neutrophil survival, cause the airways to become loaded with neutrophils explaining the increase in induced sputum [17,18].

An increase in oxidative stress markers including nitric oxide (NO), hydrogen peroxide, and lipid peroxidation products has been reported in COPD [19-21]. In severe cases, the disturb in oxidative stress causes enhancement of activity and/or expression of enzymes like inducible NO synthase (NOS_2) and neuronal NOS (NOS1), increasing NO and H_2O_2 production in lung [22,23]. Unlike patients with mild asthma, who exhale high levels of NO, COPD patients exhale near normal NO levels but during exacerbations NO levels increase [23-25]. It has been suggested that this NO increase

might be related to the formation of nitrotyrosine adducts, also increased in COPD [26]. On the other hand, H_2O_2 production leads to endothelial dysfunction, atherosclerosis, and hypertension [27,28].

It has been suggested that an autoimmune component might be involved in the pathophysiology of Pulsus paradoxus (PP), since an increase in B-cell production has been observed [19,29]. The presence of circulating antinuclear antibodies (ANA) [30], auto-antibodies against elastin, collagen V [31-33], anti-decorin antibody, and bronchial epithelial cells with IgG and C3 deposition have been described in PP lung [34,35]. In addition to this, smoking has been associated to an increase in class-switched IgG-memory B cells both in plasma and lung. A recent study indicated that COPD patients present autoantibodies against many different self-antigens that were mainly oxidative stress-modified self-proteins [19,36].

Several studies have demonstrated that the importance of the detection of P pulmonale in the ECG, and have correlated it with COPD severity and indication of life long oxygen therapy. In this regard, previous studies have shown variable P pulmonale percentages such as Lazović B (14.5%) [37], Banker H (35%) [38], Mod JS., *et al.* (45%) [39], Nalabothu SK (20%) [40] and Vineeth A (52.5%) [41].

In our study, 128/364 patients presented P pulmonale (35.16%). In another study by Reddy., et al. [42] described other findings like atrial ectopics, ventricular ectopics, incomplete RBBB, complete RBBB, and atrial fibrillation and other arrhythmias, which were observed in more than 50% of their patients. Less common findings included ST segment depression in lead II, III, aVF, T wave inversion in leads V1-V3, RBBB, S wave in lead I sign, ventricular ectopics, multifocal atrial tachycardia and S-I, S-II, S-III pattern4, which are usually observed in moderate COPD. A study by Sharma., *et al.* [43] showed that P pulmonale could be an indicator of severe COPD with only few false positives. The combination of rS pattern in lead V5-V6, right axis deviation, clockwise rotation, dominant R in lead aVR and P pulmonale were indicative of right ventricular hypertrophy (RVH) in patients lacking classical RVH changes in ECG [39].

In our study, tachycardia was observed in 113 patients (31.04%), bradycardia in 9 (2.47%) and 247 (66.86%) presented normal heart rate. Right axis deviation was found in 77 patients (21.15%), left axis deviation in 39 (10.17%), vertical deviation in 1 (0.27%) and 247 (66.86%) were found to be normal. Vertical heart positioned patients included 87 cases (23.90%), horizontal 38 cases (10.44%), and 239 cases (65.66%) were found normal. Furthermore, low voltage was observed in 20 patients (5.49%). Incomplete RBBB was found in 64 patients (17.58%) and complete RBBB was reported in 2 cases (0.55%). ST changes were observed in 146 cases (40.11%). Tall RV1 was observed in 42 cases (11.54%) and Deep SV6 was detected in 169 patients (46.43%).

In the study conducted by Bunker, vertical heart position was observed in 65% of the patients [38]. Also, 65% of patients in this study showed dominant S wave in V5 and V6 and in our study only 46.43% showed this sign in ECG. Interestingly, Mod., *et al.* [39] revealed that electrocardiographic changes in chronic cor pulmonale are due to vertical position of the heart, RVH or both.

Conclusion

Present study shows high incidence of BB phenotype in 51 - 65 age group COPD patients. Therefore, there is a need for implementing its routine assay in COPD patients, particularly in those patients whose conditions are critical to manage. A proper therapeutic management can prevent the disease progression to atherosclerosis and hypertension, relieve symptoms, improve exercise tolerance and health status, and reduce complications and exacerbations, overall decreasing the disease mortality rate.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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