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''DETERMINE THE RELATIONSHIP BETWEEN ARRYTHMIA OCCURRENCE AND THE SEVERITY OF COPD''

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Abstract:

Introduction- Chronic obstructive pulmona1y disease (COPD) is a prevalent respiratory condition characterized by airflow limitation that is not completely reversible, with a forced expiratory volume in one second to forced vital capacity (FEVl/FVC) ratio of less than 70%. It ranks as the fom1h leading cause of mortality worldwide, following myocardial infarction, cancer, and stroke. COPD is associated with significant morbidity and mortality, and cardiovascular events have been identified as the leading cause of death in COPD patients

Aims Objective: This prospective cohort study aimed to investigate ''determine the relationship between arrythmia occurrence and the severity of COPD''.

Methods: The study included 100 diagnosed cases of COPD, divided into stable COPD and acute exacerbations. Routine blood investigations, electrocardiogram (ECG), 2D echocardiography, and 24-hour Holter monitoring were conducted to assess cardiac rhythm disturbances. The type of arrhythmia was noted for each patient. Statistical analysis was performed using SPSS 26 software.

Results: Among the COPD patients, 53% had supraventricular ectopic, 20% had atrial tachycardia, 16% had conduction abnormalities, and 10% had ventricular ectopics. Males had a higher prevalence of COPD and arrhythmias compared to females. ECG abnormalities associated with right heart dysfunction, such as P-pulmonale, right ventricular hypertrophy (RVH), and right bundle branch block (RBBB), were more prevalent in patients with severe COPD. Sinus tachycardia was more common in severe COPD patients.

Conclusion: The study findings highlight the relationship between COPD severity and the presence of arrhythmias. Patients with severe COPD had a higher incidence of ECG abnormalities associated with right hea11 dysfunction. The prevalence of arrhythmias in COPD patients was estimated at 12-14%, with supraventricular ectopics and atrial tachycardia being the most common types observed. Understanding the prevalence and types of arrhythmias in COPD patients can guide appropriate monitoring and interventions to reduce arrhythmia-related complications.

Keywords: Chronic obstructive pulmonary disease, arrhythmias, Holter monitoring, COPD severity, right heart dysfunction.

INTRODUCTION

In both developed and developing countries, chronic obstructive pulmonary disease (COPD) is a prominent cause of illness and death [1]. According to major studies [2,3], cardiovascular events are the leading cause of COPD-related death, and there is some evidence that arrhythmias may play a role in some of these events [4]. Patients with both stable [5] and worsened COPD [6,7] might develop atrial or ventricular rhythm abnormalities, which can increase the risk of sudden death [6,7].

GOLD (guidelines for obstructive lung disease) defines chronic obstructive pulmonary disease (COPD) as a clinical condition characterizedby airflow limitation that is not totally reversible, with FEV1/FVC 70%. Chronic bronchitis and emphysema are two types of COPD. It is the world's fourth biggest cause of mortality, trailing only myocardial infarction, cancer, and stroke. According to multiple studies, cardiovascular problems, includingarrhythmias, caused a significant number of mortalities in patients with moderate COPD, particularly in younger people.

In 69 percent of cases, supraventricular tachycardia was present. Repetitive ventricular arrhythmia was found in 64% of the patients, and it wasmuch more common in men and those with oedema or high PCO2. In 35% of the patients, the ventricular premature beats were greater than or equivalent to 25 per hour. Arrhythmias in COPD are likely complex, involving a number ofrisk factors such as hypoxia, acidosis, and a reduction in FEV1. In stable COPD patients, a lower FEV1 is an independent predictor of new onset atrial fibrillation.

The occurrence of arrhythmias in COPD sufferers is predicted to be 12-14 percent [8,9]. Arrhythmias may be because of different comorbidities, together with coronary heart sickness, hypertensive coronary heart sickness, proper and/or left ventricular failure, hypokalaemia and hypomagnesaemia, digoxin, or macrolide antibiotics [10]. COPD and arrhythmias have not unusual place hazard factors, together with older age and smoking, and arrhythmias may be because of different comorbidities, together with coronary heart sickness, hypertensive coronary heart sickness There were no times of arrhythmias in spite of research of ischemic coronary heart sickness after bronchodilation and smoking interplay in COPD [11]. Arrhythmias produced with the aid of using bronchodilators, in particular, have garnered a whole lot of attention; recently, to keep away from deadly arrhythmia, important cautions were issued earlier than administering bronchodilators[12,13,14].

n a study using outpatient ECG monitoring, it occurred in 83% of patients with premature ventricular contractions, 68% with premature ventricular contractions, 61% with premature ventricular contractions, and 22% with persistent ventricular tachycardia. Did.

In acute exacerbations and stable COPD, arrhythmias were found to be associated with increased mortality. Therefore, the detection and analysis of COPD arrhythmias is important. Halter monitoring continuously records the rhythm of the heart during walking. Therefore, it can improve the ability to observe the rhythm of the heart during symptoms and detect arrhythmias in asymptomatic patients.

The condition affects the likelihood of arrhythmias in patients with COPD and increases the incidence of supraventricular tachycardia when it worsens (1, 2, 5). Arrhythmias are common even in people with stable COPD6, and are not uncommon in atrial fibrillation (AF). Monitoring patients admitted to the hospital for COPD in clinical practice. Atrial fibrillation is the most common arrhythmia in the elderly, but little research has been done on the relationship between lung function and the likelihood ofdeveloping atrial fibrillation. It is important to study the relationship between lower lung function and atrial fibrillation, as the incidence of COPD can increase. The incidence of COPD is projected to increase dramatically in the future, reflecting previous smoking practices in an aging society7,8, and the relationship between decreased lung function and atrial fibrillation can be investigated. It is important.

The aim of this study was to estimate the prevalence and types of arrhythmias in COPD patients and to correlate them with severity and presence of right heart failure and acute exacerbations. This would impact management of COPD patients.

AIMS & OBJECTIVES

Aims:

This study was be a prospective cohort study conducted in the Department of Medicine at J.A. Group of Hospitals, Gwalior, from June 2020 to June 2021. The aim of this study is **''determine the relationship between arrythmia occurrence and the severity of COPD''.**

Materials and Methods:

Study Population:

The study was including diagnosed cases of COPD between 30-60 years of age attending the Department of Medicine at J.A. Group of Hospitals. The sample size was consisting of 100 COPD cases, which was be divided into two groups: stable COPD and acute exacerbations.

Data Collection:

All patients included in the study were undergo routine blood investigations, including hemogram, erythrocyte sedimentation rate, blood sugars, renal function tests, liver function tests, electrocardiogram (ECG), and 2D echocardiography. Subsequently, 24-hour Holter monitoring was be performed using the Release 2.9 Digitrak XT Philips machine to record the cardiac rhythm disturbances. The type of arrhythmia was noted for each patient.

Statistical Analysis:

The collected data was be compiled and analyzed using SPSS 26 software. Graphs was generated using Microsoft Excel and Word. A p-value of less than 0.05 was considered statistically significant.

Inclusion Criteria:

All confirmed cases of COPD (including known cases as well as newly diagnosed cases) between the ages of 30 to 60 years, diagnosed based on the Revised GOLD criteria, and attending the Department of Medicine at J.A. Group of Hospitals during the study period from June 2020 to June 2021 was included in the study.

Exclusion Criteria:

1. Patients below 30 years and above 60 years of age.
2. Patients with ischemic hea1i disease or structural heart. disease diagnosed on ECG and 2D echocardiography.
3. Patients with other lung diseases such as interstitial lung disease, pneumonia, and active tuberculosis diagnosed on chest X-ray, sputum microscopy, and pulmonary function tests.
4. Patients on medications known to cause arrhythmias, other than those prescribed for COPD.

OBSERVATIONS

-In the present study, Total 100 male and female patients were included in thestudy among which 20 patients were female (20%) and 80 patients were male(80%).

-Out of 100 patients, maximum cases belonged to age group 61-70 years (n=37), followed by 51-60 years (n=29). Mean age of the cases was 61.18 years with standard deviation of 9.59.

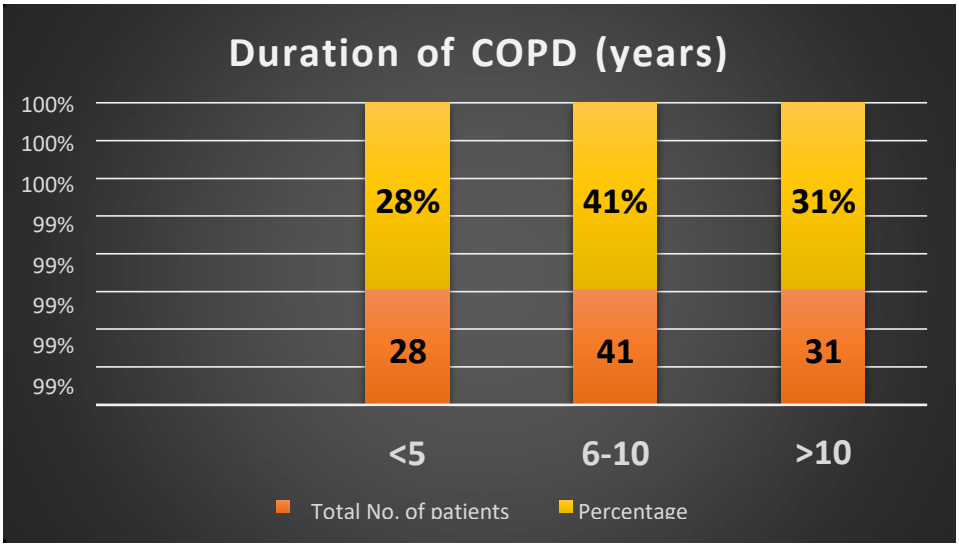
--Out of 80 male patients, maximum belonged to the age group 61-70 years (n=29). Out of 20 female patients, maximum belonged to the age group 61-70years (n=8).

Table 1: Distribution of patients on basis of disease severity(GOLD staging)

GOLD Staging	Total No. of patients (n)	Percentage (%)	
I	12	12	40
II	28	28	
III	29	29	60
IV	31	31	
Total	100	100	

Out of 100 patients, maximum number of patients belonged to GOLD stage III (n=33), while 28 patients were in GOLD stage II, 27 patients in GOLD stage IV and least number of patients were in GOLD stage I (n=12), which may also imply that patients do not seek medical advice in early stages of the disease leading to delay in treatment and increased complications.

-Out of 100 patients, 41 patients had duration of illness between 6 to 10 years, 31 patients had duration of illness > 10 years while 28 patients had durationof <5 years. The mean duration of COPD was 9.21 years with standard deviation of 6.04.



Graph : showing distribution of patients on the basis ofduration of illness

Table 2 : Showing Demographic and spirometry variables instudy population according to the GOLD classification

Variables	Total no. of subjects(n=100)	GOLD I/II(n=40)	GOLD III/IV(n= 60)	p-value
Gender (M/F)	80/20	31/9	49/11	0.6098
Mean Age (years)	61.18±9.59	57.95±7.97	63.33±9.96	0.037
Mean duration (years)	9.21±6.04	6.57±4.14	10.97±6.45	<0.001
PFT				
FVC (L)	2.96±1.03	3.5±1.1	2.2±0.5	<0.01
FEV_1(L)	1.98±0.77	2.5±0.7	1.24±0.2	<0.001
FEV_1/FVC (%)	57.02±6.97	62.07±4.72	53.65±6.13	<0.001
SpO_2(%)	95.5±2.2	96.2±1.2	90+-0.85	<0.001

-Above table is showing the correlation of severity of COPD (as per GOLD staging) with the age of the patients, value of Chi-square test being 8.4587 and p-value being 0.0374, which is statistically significant showing that severity of COPD is directly related to the age of the patient.

Table 3 : Showing correlation of severity of disease (as perGOLD staging) with the duration of illness

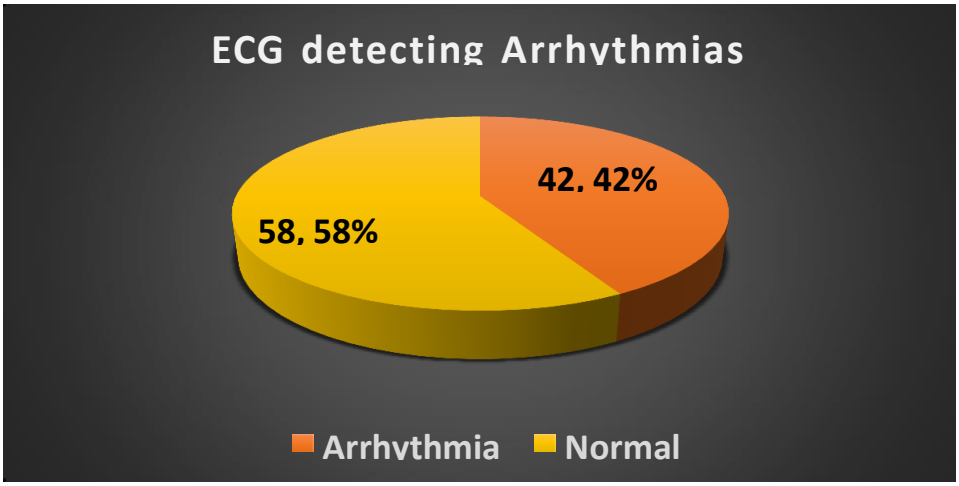
Duration of COPD(years)	Total No. ofpatients	GOLD I/II	GOLD III/IV
<5	28	19	9
6-10	41	17	24
>10	31	4	27
Total	100	40	60
Mean duration (years)	9.21±6.04	6.57±4.14	10.97±6.45
Chi-square test	**18.574**		
p-value	**<0.001**		

Above table is showing the correlation of severity of COPD (as per GOLD staging) with duration of the illness. Mean duration is 6.57± 4.14 years in GOLD stage I/II as compared to 10.97±6.45 years in GOLD stage III/IV, value of Chi-square test being 18.574 and p-value being <0.001, whichis statistically significant showing that severity of COPD is directly related to the duration of the illness.

Table 4: Distribution of patients on the basis of ECG detectingArrhythmias

ECG	Total No. of patients(n=100)	Percentage(%)
Arrhythmia	42	42%
Normal	58	58%
Total	100	100%

In present study, Out of 100 patients 42 (42%) have Arrhythmia inECG and 58% have Normal ECG.

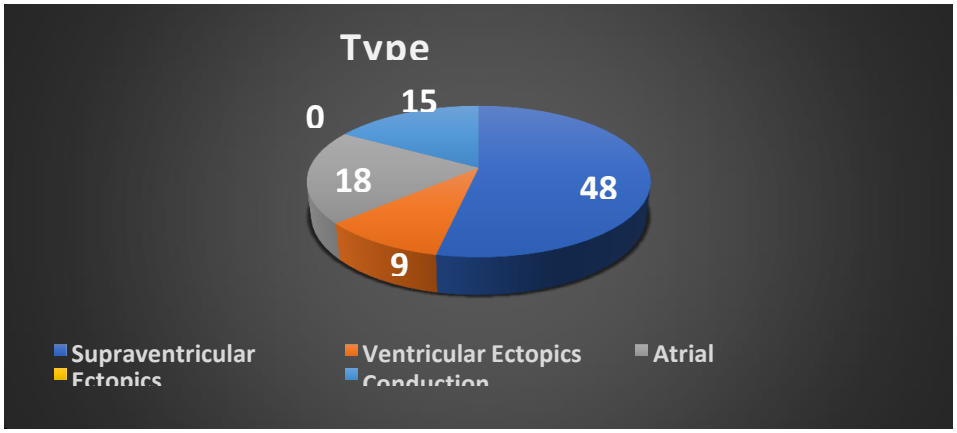


Graph : Distribution of patients on the basis of ECG detectingArrhythmias

Table 5: Distribution of COPD patients according to type ofarrhythmia in Holter monitoring

Type Arrhythmia	Number of Patients (N=100)	Percent
Supraventricular Ectopics	48	48%
Ventricular Ectopics	9	9%
Atrial Tachycardia	18	18%
Ventricular Tachycardia	0	0%
Conduction Abnormality	15	15%

In our study, 48% patients had Supraventricular Ectopics arrhythmia followed by 18% had Atrial tachycardia followed by 15% had conduction Abnormality then 9% had Ventricular Ectopics.



Graph : Distribution of COPD patients according to type ofarrhythmia in Holter monitoring

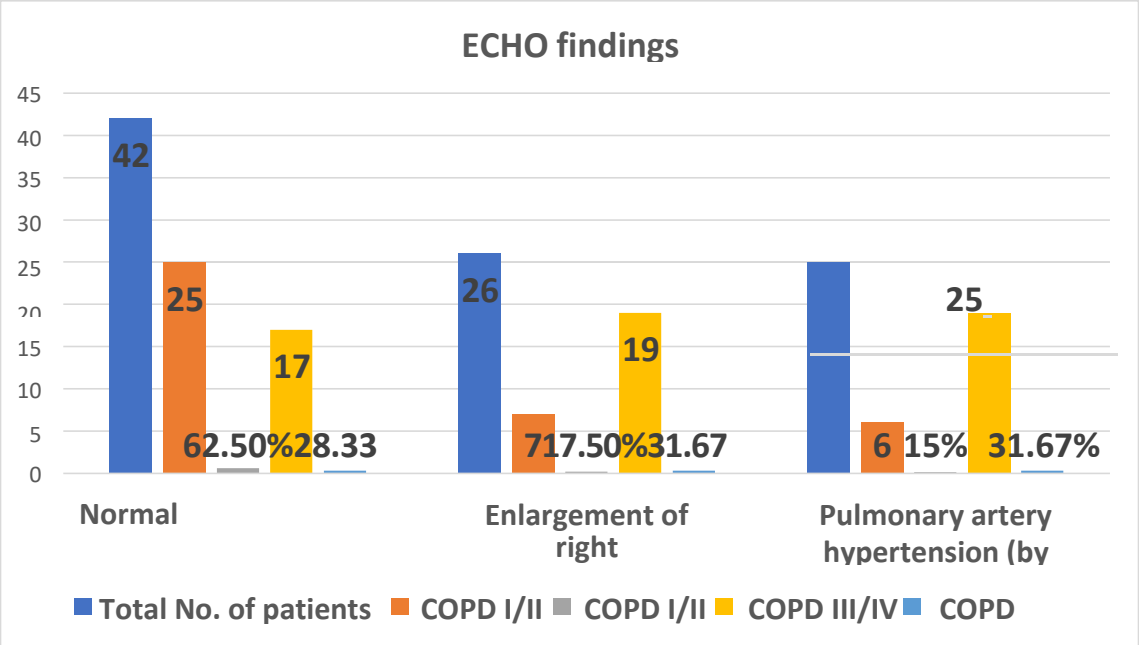
Table 6 : Showing Electrocardiographic changes in patients ofCOPD according to disease severity

ECG findings	Total No. of patients	COPD I/II (n=40)		COPD III/IV (n=60)	
		No.	%	No.	%
Normal electrocardiogram	36	25	62.5	11	18.3
Sinus tachycardia	14	4	10%	10	16.6%
P-Pulmonale +Right atrial enlargement+ Rightventricular hypertrophy (RVH)	43	10	25%	33	55%
P-Pulmonale + Rightventricular hypertrophy(RVH) + Right bundle branch block (RBBB)	7	1	2.5%	6	10%

- Out of 100 patients, 36 had **normal ECG findings**, of which 25 (62.5) belonged to mild category (GOLD stage I/II) and 11(18.3%) belonged to moderate-severe category (GOLD stage III/IV).
- Out of total 40 patients in GOLD stage I/II, 62.5% had normal ECG (n=25) while among 60 patients in GOLD stage III/IV, only 18.3% had normal ECG (n=11).
- ECG abnormalities showing **Right heart dysfunction like P- pulmonale +RVH +RBBB** and **P-Pulmonale +Right atrial enlargement+ Right ventricular hypertrophy (RVH)** were significantly higher in patients with GOLD stage III/IV (i.e. 10% and 55%) as compared to patients with GOLD stage I/II (i.e.2.5% and 25%).
- ECG abnormalities showing **Sinus tachycardia** were significantly higher in patients with GOLD stage III/IV (i.e. 16.6%) as compared to 10% in patients with GOLD stage I/II.

Table 7: Showing Echocardiographic evaluation of COPDpatients according to disease severity

ECHO findings	Total No. of patients(N=100)	COPD I/II(n=40)		COPD III/IV(n=60)	
		No.	%	No.	%
Normal echocardiogram	49	27	**67.5**	22	**36.66**
Enlargement of right cardiac chambers	26	7	**17.5**	19	**31.67**
Pulmonary artery hypertension	25	6	**15**	19	**31.67**



Graph: Showing Echocardiographic evaluation of COPDpatients according to disease severity

- Out of 100 patients, 42 had normal ECHO findings, of which 25 belonged to mild category (GOLD stage I/II) and 17 belonged to moderate-severe category (GOLD stage III/IV).
- Out of total 40 patients in GOLD stage I/II, 62.5% had normal ECHO (n=25) while among 60 patients in GOLD stage III/IV, only 28.33% had normal ECHO (n=17).
- ECHO abnormalities showing Right heart dysfunction like Right cardiac chamber enlargement and Pulmonary artery Hypertension werefound to be significantly higher in patients with GOLD

stage III/IV (i.e.31.67% each) as compared to patients with GOLD stage I/II (i.e. 17.5% and 15% respectively).

Table 8: Association between Gold Stage and ECG Changes

ECG Changes	Gold Stage				Total
	I	II	III	IV	
Normal	8 (21.6%)	17(45.9%)	4(11.1%)	8(21.6%)	36(100%)
Tachycardia	2 (14.3%)	2(15.4%)	8(57.1%)	2(14.3%)	14(100%)
P-Pulmonale + RVH	0(0%)	2(16.7%)	7(58.3%)	3(25%)	12(100%)
P-Pulmonale	2(6.7%)	6(20%)	12(40%)	10(33.3%)	30(100%)
P-Pulmonale + RVH+ BBB	0(0%)	1(14.3%)	(28.6%)	4(57.1%)	7(100%)
Chi Square Value= 27.667		Df-12	P-Vale-0.006		100(100%)

Discussion:

Chronic Obstructive Pulmonary Disease (COPD) is a complex disease that not only affects the lungs but also has systemic effects on various organs, including the heart. Cardiovascular complications, including cardiac arrhythmias, are common in COPD patients due to shared risk factors and the systemic inflammatory response associated with the disease[9 11]

In our study, we found that males had a higher prevalence of COPD and arrhythmias compared to females, with a male-to-female ratio of 4:1. This finding is consistent with previous studies that have shown a higher prevalence of COPD in males, which can be attributed to factors such as smoking and occupational exposure to pollutants (Zaghla et al., Demissie et a1.)1[2]-l3_

Electrocardiographic (ECG) findings revealed that 42% of the patients in our study had arrhythmias, while 58% had normal ECG results. Among the patients with normal ECG findings, a majority belonged to the mild category of COPD (GOLD stage I/II), indicating a possible association between the severity of COPD and the presence of arrhythmias. In contrast, patients in the moderate-severe category (GOLD stage III/IV) had a higher incidence of ECG abnormalities associated with right heart dysfunction, such as P-pulmonale, right ventricular hype11rophy (RVH), and right bundle branch block (RBBB). Additionally, sinus tachycardia was more prevalent in patients with severe COPD.

These findings are consistent with previous studies that have reported similar ECG abnormalities in COPD patients, including P-pulmonale and sinus tachycardia (Dabadghao et al.,Warnier et al.). The presence of these ECG abnormalities suggests underlying cardiac dysfunction and highlights the impact of COPD severity on cardiac function[14 15]

However, it is important to note that the association between COPD severity and arrhythmias is complex and multifactorial. Factors such as systemic inflammation, hypoxia, hypercapnia, and autonomic dysregulation in COPD can contribute to the development of arrhythmias. Further studies are needed to elucidate the underlying mechanisms and the specific impact of each factor on arrhythmia occurrence in COPD patients.

Conclusion:

The findings of tl1is study contribute to our understanding of the impact of COPD severity on arrhythmia development. In the study population, both stable COPD and acute exacerbations were associated with an increased risk of developing atrial or ventricular rhythm abnormalities. The prevalence of arrhythmias in COPD patients was estimated to be around 12-14%, with supraventricular ectopics and atrial tachycardia being the most common types observed.

The study results revealed that tl1ere is a relationship between the severity of COPD and the presence

of arrhythmias. Patients with more severe COPD, classified as GOLD stage III/IV, had a higher incidence of electrocardiographic (ECG) abnormalities associated with right heart dysfunction, including P-pulmonale, right ventricular hypertrophy (RVH), and right bundle branch block (RBBB). Additionally, sinus tachycardia was more prevalent in patients with severe COPD. These ECG abnormalities suggest underlying cardiac dysfunction, highlighting the impact of COPD severity on cardiac function.The association between COPD severity and arrhythmias is likely multifactorial, involving factors such as systemic inflammation, chronic hypoxia, acidosis, and a decrease in lung function. Further research is needed to elucidate the specific mechanisms underlying arrhythmia occurrence in COPD patients and the contribution of each factor.

Understanding the prevalence and types of arrhythmias in COPD patients, as well as their association with disease severity, is crucial for effective management and improved patient outcomes. This knowledge can guide healthcare professionals in implementing appropriate monitoring strategies and interventions to reduce the risk of arrhythmias and associated complications in COPD patients.

Based on the study findings, it is recommended that healthcare providers involved in the care of COPD patients prioritize cardiac assessment, including ECG, particularly in patients with severe COPD. Regular monitoring for arrhythmias can help identify and manage cardiac abnormalities, potentially leading to improved patient outcomes.

Targeted interventions may be developed based on the specific arrhythmia types observed in COPD patients. For example, patients with supraventricular ectopics may benefit from medications or interventions targeting atrial fibrillation/flutter, while those with atrial tachycardia may require specialized treatment options. Further research is warranted to explore the efficacy of different interventions and their impact on reducing the burden of arrhythmias in COPD patients.

In conclusion, this study provides valuable insights into the pattern of arrhythmias in COPD patients and their association with disease severity. The findings underscore the importance of cardiac assessment in the management of COPD patients, particularly those with severe disease. By identifying and monitoring arrhythmias, healthcare providers can better understand the impact of these cardiac abnormalities on the clinical course and prognosis of COPD patients, leading to more targeted interventions and improved patient outcomes.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. WorkshopReport, Global Strategy for Diagnosis, Management and Prevention of COPD. Updated September 2004. http://www .goldcopd.org/ (accessed October 19, 2014).
2. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD: COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest 2005;128:2068-2075.External Resources Pubmed/Medline (NLM) Crossref (DOI)
3. Maclay JD, MacNee W: Cardiovascular disease in COPD:mechanisms. Chest 2013;143:798-807.External ResourcesPubmed/Medline (NLM) Crossref (DOI)
4. Schneider C, Bothner U, Jick SS, Meier CR: Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur J Epidemiology 2010;25:253-260.External Resources Pubmed/Medline (NLM) Crossref (DOI)
5. Konecny T, Park JY, Somers KR, Konecny D, Orban M, Soucek F, Parker KO, Scanlon PD, Asirvatham SJ, Brady PA, Rihal CS: Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias. Am J Cardiol 2014;114:272-277.External Resources Pubmed/Medline (NLM) Crossref (DOI)
6. Shih HT, Webb CR, Conway WA, Peterson E, Tilley B, Goldstein S: Frequency and significance of cardiac arrhythmias in chronic obstructive lung disease. Chest 1988;94:44-48.External Resources Pubmed/Medline (NLM) Crossref (DOI)

7. Steer J, Gibson GJ, Bourke SC: Predicting outcomes following hospitalization for acute exacerbations of COPD. QJM 2010;103:817- 829.External Resources Pubmed/Medline (NLM) Crossref (DOI)
8. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL: Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005;128:2099-2107.External Resources Pubmed/Medline (NLM)Crossref (DOI)
9. Mapel DW, Dedrick D, Davis K: Trends and cardiovascular co- morbidities of COPD patients in the Veterans Administration Medical System, 1991-1999. COPD 2005;2:35-41.External ResourcesPubmed/Medline (NLM)Crossref (DOI)
10. Albert RK, Schuller JL; COPD Clinical Research Network: Macrolide antibiotics and the risk of cardiac arrhythmias. Am J Respir Crit Care Med 2014;189:1173-1180.External Resources Pubmed/Medline(NLM) Crossref (DOI)
11. van Dijk WD, Lenders JWM, Holtman J, Grootens J, Akkermans R, Heijdra Y, van Weel C, Schermer TRJ: Bronchodilation and smoking interaction in COPD: a cohort pilot study to assess cardiovascular risk. Respiration 2012;83:125-132.External Resources Pubmed/Medline (NLM) Crossref (DOI)
12. Chowdhury BA, Seymour SM, Levenson MS: Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. N Engl J Med2011;364:2473-2475.External ResourcesPubmed/Medline(NLM) Crossref (DOI)
13. Bhatt SP, Dransfield MT: Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013;162:237-251.External Resources Pubmed/Medline (NLM) Crossref (DOI)
14. Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, Stukel TA: Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med 2013;173:1175-1185.External Resources Pubmed/Medline (NLM)Crossref (DOI)
15. Thomas L Petty. The history of COPD. International Journal of COPD 2006; 1(1):3-14.
16. Swash M, Glynn M. Hutchinson's Clinical methods. 22nd ed. Chapter 6. In: Respiratory System. London: Elsevier Company. p. 58.
17. Maria L Padilla. Pulmonary Circulation. Chest 2003;124:1183.
18. William F Ganong. Pulmonary function. 22nd ed. Chapter 34. In: Review of Medical Physiology. New York: The McGraw-Hill Companies pp. 628-9.
19. Victor I Peinado, Sandra Pizarro, Joan Albert Barbera. Pulmonary Vascular Involvement in COPD; CHEST 2008;134:808-14.
20. Celli BR, Macnee W, Agusti A. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. EurRespir J 2004;23:932-46.
22. William Macnee. Chronic bronchitis and emphysema. 5th ed. Chapter
23. In: Crofton and Douglas's respiratory disease, AnthonySeaton,Douglas, eds. Oxford: Blackwell Science Publishers; 2000. pp. 616-79.
23. Viegi G, Pistelli F, Sherrill DL. Definition, epidemiology and natural history of COPD. EurRespir J 2007;30:993-1013.
24. David M Mannino. COPD. Chest 2002;121:121S-126S.
25. Fletcher CM, Pride NB. Definitions of emphysema, chronic bronchitis, asthma, and airflow obstruction: 25 years on from the Ciba symposium.Thorax 1984;39:81-5.
26. Koul PA, Hakin NA, Malik SA, Khan UH, Patel J, Gnatiuc L, Burney PJ. Prevalence of chronic airflow limitation in Kashmir, North India: results from the BOLD study. Int J Tuberc LUng Dis 2016;20:1399- 1404.
27. Burney P, Jithoo A, kato B, janson C, Mannino D, Nizankowska-Mogilnicka E, Studnicka M, Tan W, Bateman E, Kocabas A, vollmer WM, Gislason T, Marks G, Koul PA, Harrabi I, Gnautic L, Buist S. Burden of Obstructive Lung Disease (BOLD) Study. Chronic obstructive pulmonary disease mortality and prevalence: theassociations with smoking and poverty- a BOLD analysis. Thorax 2014;69:465-73.
28. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths,

prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Respiratory Medicine August 17, 2017.
29. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. Annual review of pathology 2009; 4: 435-59.
30. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016; 138(1): 16-27.
31. Sze MA, Dimitriu PA, Suzuki M, et al. Host Response to the Lung Microbiome in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2015; 192(4): 438-45.
32. Lee SH, Goswami S, Grudo A, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nature medicine 2007; 13(5): 567-9.
33. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD--implications and relevance for treatment. Int J Chron Obstruct Pulmon Dis 2014; 9: 1207-24.
34. Malhotra D, Thimmulappa R, Vij N, et al. Heightened endoplasmic reticulum stress in the lungs of patients with chronic obstructive pulmonary disease: the role of Nrf2-regulated proteasomal activity. AmJ Respir Crit Care Med 2009; 180(12): 1196-207.
35. Stockley RA. Neutrophils and protease/antiprotease imbalance. Am J Respir Crit Care Med 1999; 160(5 Pt 2): S49-52.
36. Johnson SR. Untangling the protease web in COPD: metalloproteinasesin the silent zone. Thorax 2016; 71(2): 105-6.
37. Polosukhin VV, Richmond BW, Du RH, et al. Secretory IgA Deficiency in Individual Small Airways Is Associated with Persistent Inflammation and Remodeling. Am J Respir Crit Care Med 2017;195(8): 1010-21.
38. Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. Clin Chest Med 2014; 35(1): 71-86.
39. Katzenstein AL, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Human pathology 2008; 39(9): 1275-94.
40. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes andemphysema in smokers with interstitial lung abnormalities. N Engl J Med 2011; 364(10): 897-906.
41. Putman RK, Hatabu H, Araki T, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. Jama 2016; 315(7): 672- 81.
42. Churg A, Tai H, Coulthard T, Wang R, Wright JL. Cigarette smoke drives small airway remodeling by induction of growth factors in the airway wall. Am J Respir Crit Care Med 2006; 174(12): 1327-34.
43. Rennard SI, Wachenfeldt K. Rationale and emerging approaches for targeting lung repair and regeneration in the treatment of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2011; 8(4): 368- 75. 43. Hogg JC, McDonough JE, Gosselink JV, Hayashi S. What drives the peripheral lung-remodeling process in chronic obstructive pulmonary disease? Proc Am Thorac Soc 2009; 6(8): 668-72.
44. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. Nature reviews Immunology 2008; 8(3): 183-92.
45. Global Initiative for Asthma. 2015 Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). 2015 (accessed 14 October 2018).
46. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004; 350(26): 2645-53.
47. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstructionand emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011; 365(17): 1567-75.
48. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008; 177(6): 622-9.
49. Elbehairy AF, Ciavaglia CE, Webb KA, et al. Pulmonary Gas Exchange Abnormalities in Mild

Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. Am JRespir Crit Care Med 2015; 191(12): 1384-94.
50. Casaburi R, Maltais F, Porszasz J, et al. Effects of tiotropium onhyperinflation and treadmill exercis e tolerance in mild to moderate chronic obstructive pulmonary disease. Annals of the American Thoracic Society 2014; 11(9): 1351-61.
51. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation -perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol 2009; 106(6): 1902-8.
52. Burgel PR, Nadel JA. Epidermal growth factor receptor-mediated innate immune responses and their roles in airway diseases. Eur Respir J 2008; 32(4): 1068-81.
53. S.P. Bhatt, M.T. Dransfield, Chronic obstructive pulmonary disease and cardiovascular disease, Transl. Res. 162 (2013) 237–251.
54. M. Decramer, W. Janssens, M. Miravitlles, Chronic obstructive pulmonary disease, Lancet 379 (2012) 1341–1351.
55. S.M. Curkendall, C. DeLuise, J.K. Jones, et al., Cardiovascular disease in patients with chronic obstructive pulmonary disease: Saskatchewan Canada cardiovascular disease in COPD patients, Ann. Epidemiol. 16 (2006) 63–70. [56] F.H. Rutten, M.J. Cramer, D.E. Grobbee, et al., Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease, Eur. Heart J. 26 (2005) 1887–1894.
57. S.K. Agarwal, G. Heiss, R.G. Barr, et al., Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study, Eur. J. Heart Fail. 14 (2012) 414–422.
58. L.M. Fabbri, F. Luppi, B. Beghe, et al., Complex chronic comorbiditiesof COPD, Eur. Respir. J. 31 (2008) 204–212.
59. H.T. Shih, C.R.Webb, W.A. Conway, et al., Frequency and significance of cardiac arrhythmias in chronic obstructive lung disease, Chest 94 (1988) 44–48.
60. J. Li, S.K. Agarwal, A. Alonso, et al., Airflow obstruction, lung function, and incidence of atrial fibrillation: the Atherosclerosis Risk inCommunities (ARIC) study, Circulation 129 (2014) 971–980.
61. Obstructive Lung Disease. Chest 94(1): 44-48.