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Prolongation of QTc interval in subjects with Chronic Obstructive Pulmonary Disease: A tool to assess the severity and optimize management.

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Abstract:
Background:*Being a systemic disease, COPD is associated with several adverse effects in various organs, the heart being one of them. QTc interval may help to assess the severity of COPD and may help in predicting those with poor prognosis. Systematic study of QTc interval in COPD patients at different severity stages may help reveal any association. Thus, the study is taken up to assess the QTc interval in COPD and assess the impact on the severity.*
Materials and Methods*:All patients fulfilling the inclusion and exclusion criteria were taken for study with informed consent. Data was collected using a validated questionnaire. Detailed history, clinical examination and necessary investigations: complete hemogram, renal function tests, serum electrolytes, electrocardiogram, 2D echocardiography, pulmonary function tests were done. QTc interval was calculated using Bazzet's formula and subjects were grouped into different stages of COPD using the GOLD criteria. Chi-Squares test and Fisher's exact test were used to assess the association.*
Results*:80% were males in the study; most of the participants were in the age group 61-70 years, with a mean age of 60.5 years. Tobacco use was only reported in male patients. The majority of the subjects were in Stage 2 and Stage 3 COPD. Prolonged QTc interval was present in 70% of the subjects. There was a significant association between hypoxia and prolonged QTc interval (P<0.05); COPD was associated with prolonged QTc interval (P<0.001).*
Conclusion:*The study concluded that QTc interval prolongation is associated with COPD and that the incidence of QTc interval prolongation increases with COPD severity. QTc interval prolongation increases with the severity of hypoxia and hypoxia is more with severe and very severe stages of COPD. There is increased cardiovascular morbidity and mortality in patients with severe and severe forms of COPD with hypoxia and prolonged QTc interval. Home oxygen therapy plays an important role in reducing hypoxia and associated morbidity and mortality.*

Keywords: *Chronic obstructive pulmonary disease, hypoxia, QTc interval*

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I. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of death in the world and is projected to be the third leading cause of death in the world by 2020, according to the global burden of diseases (GBD) study. The World Health Organization (WHO) has estimated that Chronic Obstructive Pulmonary Disease caused 3.17 million deaths in 2015, which accounted for 5%. It is known that 90% of COPD deaths occur in middle- and low-income countries. In India, 11% of deaths were attributed to chronic respiratory diseases in 2018[1]. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) has classified COPD into five stages based on spirometry and clinical features. The stages range from at risk (0), to mild (1), moderate (2), severe (3) and very severe (4)[2]. Altered cardiac repolarization is seen to be more prevalent in COPD patients and is a risk factor for sudden cardiac death.[3]QTc interval is calculated from ECG and a prolonged QTc interval is associated with severe forms of COPD with increased incidence of frequent hospitalizations and the need for chronic therapy. QTc interval may help to assess the severity of COPD and may help in predicting those with poor prognosis. ECG is the only additional tool to get the QTc interval of patients[4]. Systematic study of QTc interval in COPD patients at different severity stages may help reveal any association. Even within the stages classified by GOLD criteria, subgroups may have different prognoses based on the QTc interval[5]. This study aimed to assess the QTc interval in COPD and assess the impact on the severity.

II. Materials and Methods

This cross-sectional study was carried out in the Department of Medicine, Mysore Medical College and Research Institute. A total of 100 patients fulfilling the inclusion and exclusion criteria were included in this study from January 2018 to January 2019.

Study Design: Cross sectional Study

Study Location: Department of Medicine, Mysore Medical College and Research Institute

Study Duration: January 2018 to January 2019

Sample size:100 patients

Sample size calculation: With the prevalence of QTc prolongation in COPD subjects being 20%, level of significance 5% and allowable error of 10%, sample size is estimated to be 100.

Subjects and Selection criteria:Subjects meeting the inclusion criteria were selectedconsecutively until the sample size was met.

Inclusion Criteria

1. Subjects more than 18 years of age
2. Subjects with a diagnosis of COPD

Exclusion criteria

1. Subjects with cardiac diseases.
2. Subjects with chronic kidney disease.
3. Subjects with electrolyte imbalances.
4. Subjects on drugs affecting QT interval.

Procedure Methodology

Informed consent was taken from all participants. Data was collected using a pretested proforma meeting the objectives of the study. Detailed history, clinical examination and necessary investigations: complete hemogram, renal function tests, serum electrolytes, electrocardiogram, 2D echocardiography, pulmonary function tests were done.All selected patients' history and clinical examinations were made according to the Performa within 24 hours of presentation. Spo2 was measured using a pulse oximeter. An electrocardiogram using 12 lead ECG was recorded within 24 hours of presentation and a corrected QTc interval was calculated using Bazzet's formula. Venous blood samples were collected for random glucose measurements, renal function tests, serum electrolytes, liver function tests and complete blood count. Chest X-ray was done for all patients. Pulmonary function tests were done and patients.

Statistical analysis

Data was analysed using SPSS version 23.Categorical variables are expressed in numbers and percentages. Continuous variables are expressed in mean and standard deviation. The Chi-square test is used to test the association. Fisher's exact test tests the association if the expected cell value is less than 5 in 2X2 tables. P-value <=0.05 was considered statistically significant.

III. Results

We have included 100 participants, 80 males and 20 females, in the present study. With regard to age distribution, 13(13%) were in the age group < 50 years, 26 subjects were in the age group 51-60 years, 40 subjects were in the age group 61-70 years and 21 subjects were in the age group more than 71 years. The mean age observed was 60.5 years.

Tobacco use was assessed by pack years. No females had a history of tobacco use. Among males 19 (23.8%) were in <20 pack-year,55 (68.8%) was in 21-40 pack-year and 6 (7%) were in >41 pack. Concerning oxygen saturation, 68% of subjects had an oxygen saturation of <85% in room air, 28% of subjects had a saturation between 86-90% in room air and 4% of subjects had a saturation of >91% at room air. Also, pulmonary hypertension was present in 65(65%) subjects with COPD.

Table no. 1 shows the percentages of male and female subjects in different stages of COPD. Among male subjects 40% are in stage 3 COPD and the remaining 6.3%,31.3% and 22.5% of subjects are in stages 1,2 and 4 respectively. Among female subjects 55 percent of subjects are in stage 2 whereas the remaining 30% and 15% of subjects are in stages 3 and 4 respectively.

Table no. 1 Distribution of stage of COPD Vs. Gender

Stage of COPD	Gender			
	Male		Female	
	No.	(%)	No.	(%)
1	5	6.3	--	--
2	25	31.3	11	55.0
3	32	40.0	6	30.0
4	18	22.5	3	15.0
Total	80	100.0	20	100.0

Among the total study subjects this study observed 79% of subjects had prolonged QTc intervals and 21% had normal QTc intervals.

Table no. 2 shows the distribution of age with QTc interval among male and female subjects. Among male subjects we see that 44.9% had a prolonged QTc interval in the age group of 61-70 years compared to 27.3% in the same age group having a normal QTc interval. Among females 30% in the age group >71 years had a prolonged QTC interval compared to !0% in the same group having a normal QTc interval. The difference between patients with normal QTc interval and prolonged QTc interval in different age groups was not statistically significant. (p<0.214).

Table no. 2 Association of age and QTc interval in male and female subject

Gender	Age group in years	QTc interval				P value
		Normal		Prolonged		
		No.	%	No.	%	
Male	<50	1	9.1	9	13.0	NS
	51-60	4	36.4	15	21.7	
	61-70	3	27.3	31	44.9	
	>71	3	27.3	14	20.3	
Female	<50	2	20	1	10	
	51-60	4	40	3	30	
	61-70	3	30	3	30	
	>71	1	10	3	30	

The mean QTc interval in age groups 50 years, 51-60 years, 61-70 years and >71 years was 426.8, 448.3, 465.1, 459.6 milliseconds, respectively, with SD of 19.2, 14.3, 10.8 and 13, respectively and is represented in table no. 3.

Table no 3 Mean QTc interval in each age group

Age group in years	Mean QTc interval in milliseconds	Standard deviation
<50	426.8	19.20
51-60	448.3	14.33
61-70	465.1	10.8
> 71	459.6	13.0

The association between tobacco use (in pack-years) and QTc interval observed was given in table no. 4. There was no statistically significant association observed in the present study.

Table no 4 Association of tobacco use with QTc interval in male subjects

Pack years	QTc interval				P
	Normal		Prolonged		
	No.	%	No.	%	
<20	5	45.5	14	20.3	NS
21-40	5	45.5	50	72.5	
>40	1	9.1	5	7.2	

Among male subjects, 72.5% of subjects with prolonged QTc interval had an oxygen saturation at room air of less than 85% and 4.3% of subjects with prolonged QTc interval had an oxygen saturation at room air of >91%.

Among female subjects, 80% of subjects with prolonged QTc interval had an oxygen saturation at room air of <85%. The remaining 20% of subjects with prolonged QTc intervals had an oxygen saturation of 86-90%. There was a significant correlation between oxygen saturation in room air with prolonged QTc interval with a p-value of <0.05 in both male and female subjects which is shown in table no. 5

Table no. 5 Association of SpO2 (oxygen saturation) with QTc interval in male and female subjects

Gender	SpO2 (oxygen saturation)	QTc interval				P
		Normal		Prolonged		
		No.	%	No.	%	
Male	< 85%	6	54.5%	50	72.5%	<0.05
	86-90%	4	36.4%	16	23.2%	
	>91%	1	9.1%	3	4.3%	
Female	< 85%	4	40%	8	80%	<0.05
	86-90%	6	60%	2	20%	
	>91%	--	--	--	--	

The mean QTc interval in oxygen saturation at room air of <85%, 86-90% and >91% was 465.7, 447.8, 437.5 milliseconds,respectively, with SD of 16.2, 14.5 and 25.8, respectively and is shown in table no 6.

Table no. 6. Mean QTc interval in relation to Oxygen saturation

SpO2 (oxygen saturation at room air)	Mean QTc interval in milliseconds	Standard. Deviation
<=85%	465.7	16.2
86-90%	447.8	14.5
>90%	437.5	25.8
Total	459.6	18.4

In the present study, all the male subjects with pulmonary hypertension had a prolonged QTc interval. Amongst the male subjects who did not have pulmonary hypertension, 22(66.7%) had a prolonged QTc interval, and 11(33.3%) had a normal QTc interval. In the case of female participants with pulmonary hypertension, 10 (55.6%) had a prolonged QTc interval and 8 (44.4%) had a normal QTc interval. A statistically significant association was observed between pulmonary hypertension and prolonged QTc interval with a P-value of <0.005 in male and female subjects as shown in table no 7.

Table no. 7. Association of pulmonary hypertension with QTc interval in male and female subjects

Gender	Pulmonary Hypertension	QTc interval				P
		Normal		Prolonged		
		No.	%	No.	%	
Male	Present	0	0	47	100	<0.05
	Absent	11	33.3	22	66.7	
Female	Present	8	44.4	10	55.6	<0.05
	Absent	2	100	0	0	

The mean QTc interval was 468.8 milliseconds in subjects with pulmonary hypertension than 442.6 milliseconds in subjects without pulmonary hypertension as shown in table 8; implying that subjects with pulmonary hypertension are more likely to have a prolonged period QTc interval as shown in table no. 8.

Table no. 8. Mean QTc interval and pulmonary hypertension

Pulmonary Hypertension	Mean QTc interval in milliseconds	Standard deviation
Absent	442.6	16.2
Present	468.8	14.3
Total	459.6	18.5

Concerning the distribution of COPD, among males, 60% in stage 1 COPD had a normal QTc interval and the remaining 40% of males in stage 1 had a prolonged QTc interval. In stage 2 COPD and stage 3 COPD, the percentage of males with prolonged QTc intervals was 72% and 96.9%, respectively. In stage 4 COPD, all male

subjects had a prolonged QTc interval. In females, 54.5% in stage 2 COPD had a normal QTc interval and 45.5% prolonged QTc. In stage 3, 33.3% had a prolonged QTc interval and in Stage 4, all subjects had a prolonged QTc.

Table no9. Association of Stage of COPD with prolonged QTc interval

Gender	Stage of COPD	QTc Interval				P
		Normal		Prolonged		
		No.	Percentage	No.	Percentage	
Male	Stage 1	3	60%	2	40%	<0.001
	Stage 2	7	28%	18	72%	
	Stage 3	1	3.1%	31	96.9%	
	Stage 4	0	0%	18	100%	
Female	Stage 1	0	0%	0	0%	
	Stage 2	6	54.5%	5	45.5%	
	Stage 3	4	66.7%	2	33.3%	
	Stage 4	0	0%	3	100%	

The mean QTc interval was 426.8, 448.3,465.1, 459.6 milliseconds in Stage 1, Stage 2, Stage 3 and Stage 4, respectively, with an SD of 19.2, 14.33 and 10.8, respectively, implying that QTc interval increases with increasing severity of COPD indicated by stage of COPD as shown in table no. 10.

Table no.10. Mean QTc interval and Stage of COPD

COPD stage	Mean QTc interval in milliseconds	Standard deviation
1	426.8	19.20
2	448.3	14.33
3	465.1	10.8
4	459.6	13.0

The association between QTc interval with other sociodemographic and clinical factors is assessed separately for males and females. The details are given in table 6. The results showed that the variables significantly associated with QTc interval among both males and females are SPO2, pulmonary hypertension and COPD stage.

Table no 11. Association of variables with QTc interval in males and females

Gender	Variables	Categories	QTc interval				Total	P-value
			Normal		Prolonged			
			No	%	No	%		
Male	Age(years)	< =60	5	17.2	24	82.8	29	NS
		>60	6	11.8	45	88.2	51	
	Pack years	< =20	5	26.3	14	73.7	19	NS
		>20	6	9.8	55	90.2	61	
	SPO2(%)	<=85	6	10.7	50	89.3	56	<0.05
		>85	5	20.8	19	79.2	24	
	Pulmonary Hypertension	Present	--	--	47	47	47	<0.005
		Absent	11	33.3	22	66.7	33	
	COPD stage	*Early	16	39.0	25	61	41	<0.001
		**Advanced	5	8.5	54	91	59	
Female	Age(years)	< =60	6	69	4	40	10	NS
		>60	4	40	6	60	10	

	SPO2(%)	<=85	4	33.3	8	66.7	12	<0.05
		>85	6	75	2	25	8	
	Pulmonary Hypertension	Present	8	44.4	10	66.6	18	<0.005
		Absent	2	100	--	--	2	
	COPD stage	*Early	16	39.0	25	61	41	<0.001
		**Advanced	5	8.5	54	91	59	

*stage1 and 2 **stage 3 and 4

IV. Discussion

Chronic obstructive pulmonary disease is associated with increased cardiovascular mortality and morbidity with patients experiencing sudden cardiac death and arrythmias.[6]QTc prolongation in a 12 lead ECG denotes summation of ventricular depolarization and repolarization.[7] A prolonged QTc interval may be as result of multiple factors including increased age, electrolyte abnormalities, underlying cardiovascular disease and drugs.[8] In the Rotterdam study it was concluded that a prolonged QTc interval was associated with an increased risk of death among subjects without underlying cardiac disease independent of age, sex and medication.[9]

Prior studies by Sievi et al and Nilsson et al concluded that COPD patients have a prolonged QTc interval compared to healthy controls.[3,5] The underlying reason for a prolonged QTc interval in COPD patients is attributed to many causes including but not restricted to autonomic neuropathy and hypoxia as evidenced by other studies.[10] A study by Van Oekelen et al also found that a prolonged QTc interval was associated with increased cardiovascular mortality during an acute exacerbation of COPD.[11]

In the present study we used subjects with an established diagnosis of COPD and classified them into different stages based on GOLD criteria. Majority of the subjects belonged to COPD stage 3 and 4. 79% of all subjects had a prolonged QTc interval calculated by Bazzets formula.

The mean QTc interval was 426.8 ,448.3,465.1 and 459.6 milliseconds in Stage 1,2,3 and 4 respectively with the degree of prolonged QTc interval increasing with severity of COPD.

In our study we also found hypoxia to influence QTc interval with prolonged QTc interval being more prevalent with subjects with low oxygen saturation. The mean QTc interval was 437.5.447.8,465.7 milliseconds in subjects with an oxygen saturation of >90%,86-90% and <85% respectively. This was comparable with results obtained from the study conducted by Jegan et al.[12]

As a prolonged QTc interval is a marker for cardiovascular morbidity and mortality, it is essential to identify the same in patients with COPD which can help in optimization of management.

V. Conclusion

QTc interval prolongation is associated with COPD and there is increased incidence of COPD with advanced stages of COPD thus making it an important tool to assess cardiovascular morbidity and mortality in COPD patients

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