Turk Thorac J 2022; 23(2): 97-103 DOI: 10.5152/TurkThoracJ.2022.21075

Original Article

Altered Cardiac Repolarization in Chronic Obstructive Pulmonary Disease

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Cite this article as: Alper Uğuz F, Bozkuş F, Aksu E, Atilla N, Kahraman H, Doğaner A. Altered cardiac repolarization in chronic obstructive pulmonary disease. *Turk Thorac J.* 2022;23(2):97-103.

Abstract

OBJECTIVE: Altered cardiac repolarization is an important mechanism in the development of malignant cardiac arrhythmia and in the occurrence of sudden cardiac death. It is known that the risk of cardiac arrhythmia and sudden death is increased in patients with chronic obstructive pulmonary disease. Evaluating the measurements of repolarization in the electrocardiogram may provide useful information to determine potential risks for lethal arrhythmias in the patients with chronic obstructive pulmonary disease. In the present study, we investigated the possible relationships between repolarization parameters in the electrocardio and demographic, clinical, and biochemical findings in patients with chronic obstructive pulmonary disease.

MATERIAL AND METHODS: In the present study, 35 patients with Global Initiative for Chronic Obstructive Lung Disease A-B constituted group 1 and 35 patients with Global Initiative for Chronic Obstructive Lung Disease C-D constituted group 2. Cardiac repolarization and dispersion (QTc interval and QT dispersion) were measured on 12-lead electrocardiogram. QTc interval, QT dispersion, TP-e, and Tp-e/QTc were evaluated in order to determine the patients at risk of sudden cardiac death. QTc interval >440 ms in men and >460 ms in women was considered as prolonged QTc interval.

RESULTS: QTc and QTd values were found to be statistically significantly prolonged in the group of GOLD C-D compared to the group of GOLD A-B ($P < .001$). QTc value showed negative correlation with the ratio of forced expiratory volume in 1 second to forced vital capacity and partial pressure of oxygen ($P = .030$, $r = -0.260$; $P = .006$, $r = -0.332$, respectively). No significant difference was in Tp-e and Tp-e/QTc between the groups ($P = .73$, $P = .12$, respectively).

CONCLUSION: QTc and QTd are non-invasive markers reflecting arrhythmogenicity, and our findings were found to be related to prolonged QTc and QTd in patients with chronic obstructive pulmonary disease. Prolongation in the dispersion of repolarization and altered cardiac repolarization in the population with chronic obstructive pulmonary disease may be related to hypoxemia and airway obstruction. Alterations in the cardiac repolarization may put these patients at high risk for malignant ventricular arrhythmia and sudden cardiac death.

KEYWORDS: Cardiac repolarization, chronic obstructive pulmonary disease, QT interval
Received: *April 16, 2021* ***Accepted:*** *September 14, 2021*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of mortality in the world and is estimated to gain a third place by 2020. In 2012, COPD, which caused 6% of all deaths worldwide, killed over 3 million people. Chronic obstructive pulmonary disease is both a preventable and treatable disease which represents a serious public health issue. Chronic obstructive pulmonary disease is one of the main causes of chronic morbidity and mortality worldwide and considerably increases mortality rates due to its complications.[1] Most COPD patients are likely to have a previously existing cardiovascular disease and are at great risk of acute incidents, hospitalizations, and cardiovascular-related morbidity.[2,3]

Due to this strong association, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) considers cardiovascular diseases concomitant with COPD as the most significant disease and strongly recommends that COPD patients be routinely screened for cardiovascular diseases; however, they do not provide any recommendations as to how this should be done.[4]

It is known that COPD patients are at increased risk of cardiac arrhythmia and sudden death.[5-7] Remodeling of cardiac repolarization is an important mechanism in terms of the occurrence of malignant arrhythmia and sudden cardiac death.[8-10] The QT interval (QT) and QT dispersion (QTd) are electrocardiogram (ECG) parameters used to evaluate myocardial repolarization.[11] The heterogeneity and dynamics of QT interval are used to indicate increased sensitivity in ventricular arrhythmias.[12] Circadian changes may be observed in the normal heart depending on the QT interval, autonomic circulation, and increased catecholamine concentration changes.[13] The QT interval reflects homogeneity of ventricular

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repolarization. Prolonged QT interval is an indicator of cardiac repolarization abnormalities.[14]

In order to determine the potential risks of life-threatening arrhythmias, evaluation of ECG repolarization measurements will provide clinically beneficial information in this patient population. In this study, we investigated the demographic, clinical, and biochemical data of ECG repolarization indicators in COPD patients.

MATERIAL AND METHODS

The study population consisted of patients with COPD diagnosis according to the GOLD criteria and confirmed with post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) <70 criteria, who presented to the University Hospital between January 2018 and June 2018. Forced expiratory volume in 1 second (FEV1) percentage according to the expected value was used for determining the grade (1-4) of obstruction severity of COPD, as also suggested by the 2017 GOLD report. The most important revision of this report was the removal of the FEV1 value from the combined assessment. Therefore, unlike the 2011 GOLD report, A-D categories were only defined according to exacerbation risk and symptom severity. This revision completely excluded FEV1 from pharmacological treatment decision-making. On the other hand, the report emphasizes that FEV1 still remains an important factor in determining the severity and prognosis of the disease, as well as non-pharmacological treatment decision-making. In order to assess symptoms, the GOLD reports recommend the use of the COPD Assessment Test or Modified Medical Research Council Dyspnea Scale (mMRC).

Accordingly, cases followed up with COPD diagnosis for the last 5 years were classified using the GOLD criteria. The 35 cases who were GOLD A-B formed group 1 and the 35 GOLD C-D cases comprised group 2. Patients with ischemic heart disease, heart failure, acute myocardial infarction, heart valve disease, branch block in ECG, atrial fibrillation, drug use causing QT dispersion (such as probucol, terfenadine, amiodarone, erythromycin, clarithromycin), and electrolyte disorder were excluded from the study.

MAIN POINTS

- The underlying mechanisms of the relationship between chronic obstructive pulmonary disease (COPD) and sudden cardiac death are still largely unknown, and the markers of malignant cardiac arrhythmia and sudden cardiac death in COPD have not been identified.
- Prolonged QT interval and increased QT dispersion are indicators of increased risk of malignant cardiac arrhythmia and sudden cardiac death.
- Cardiac repolarization remodeling and increased repolarization dispersion may be associated with increased hypoxemia and airflow obstruction in COPD patients.
- Therefore, we believe that increased cardiovascular risk should be kept in mind when managing highly symptomatic COPD patients who undergo more frequent exacerbations.

Pulmonary function tests were performed by the same nurse on patients, who were previously informed on how it would be conducted, sitting 90 degrees upright, using a ZAN 300 spirometer. Spirometry tests were repeated at least 3 times, in which the one with the best results was used for evaluation. All study participants underwent a 12-derivation ECG, which was recorded at 50 mm/s paper speed. Electrocardiogram recording was delayed in patients with the blood pressure of 160/100 mmHg and higher. Precordial V2-V6, which best shows the QRS complex, was used for ECG measurements. Measurements were made by 2 different cardiologists, and in the case when different measurements were yielded, the average of the 2 measurements was used. The QT interval was measured as m/s units from the start of the Q wave to the point at which the T wave returned to the isoelectric line. In ECGs with U wave, the lowest point between the T and U waves was considered the end of the T wave. Derivations in which the T wave's end could not be determined were not analyzed. QT interval correction for heart rate was calculated using Bazzett's formula ($QT/\sqrt{R-R}$).

The mean of 3 consecutive corrected QT interval (QTc) in each derivation was considered the QTc interval for that derivation. Patients with QTc interval for at least 9 derivations were included in the study. Tp-e was measured as the distance between the projection of the peak of the T wave on the isoelectric line and the projection of the line connecting the descending limb of the T wave on the isoelectric line. Together with these measurements, the Tp-e/QTc ratios were also calculated. All measurements were taken manually. The correlations between clinical and laboratory results of the patients and ECG repolarization parameters were analyzed. The study was approved by the University Ethics Committee with protocol number 47 and informed written consent was obtained from all participants.

Statistical Analysis

Conformation of normal distribution of the data was tested using the Kolmogorov–Smirnov test. Data with normal distribution were compared with independent paired samples *t*-test. Group comparisons of variables without normal distribution were assessed using the Mann–Whitney *U* test. Distribution correlations of categorical variables were analyzed using the chi-squared test and Fischer's exact test. Logistic regression analysis was used to estimate QTc groups. The relationship between quantitative variables was examined with the Spearman correlation test. Statistical parameters were expressed as mean, standard deviation, median, q1 (25% quartile), and q3 (75% quartile) values. Statistical significance was accepted as $P < .05$. Data were analyzed using the International Business Machines Corporation Statistical Package for the Statistical Package for Social Sciences 22.0 (IBM SPSS Corp.; Armonk, NY, USA) package program.

RESULTS

Group 1 consisted of 35 patients who met GOLD A-B criteria, while group 2 included 35 patients who met GOLD C-D criteria. The demographic and clinical features of the groups are presented in Table 1. There was no significant difference between the groups according to age, gender, BMI, history of smoking, and mMRC score ($P = .10$, $P = .160$, $P = .92$, $P =$

.63, $P = .07$, respectively). FEV1, forced vital capacity (FVC), and FEV1/FVC levels were significantly higher in group 1 compared to group 2 ($P < .001$). The mean number of exacerbations/hospitalizations was significantly higher in group 2 compared to group 1 ($P < .001$) (Table 1).

QTc value was significantly higher in group 2 compared to group 1 ($P < .001$). Comparison of QTc values among the groups showed that 30 cases in group 1 (71.4%) were QTc negative and 5 were QTc positive (17.9%). In group 2, 12 cases were QTc negative (28.6%) and 23 were QTc positive (82.1%). Comparison of QTc positivity and negativity among the groups was statistically significant ($P < .001$) (Table 2, Figure 1). QTc value showed negative correlation with FEV1 and P_aO_2 ($P = .032$, $r = -0.257$; $P = .006$, $r = -0.332$, (Figures 2, 3) respectively). In the regression analysis of QTc and other variables, it was found that there was no correlation with age, smoking, BMI, and mMRC score ($P > .05$) and only correlated with the number of hospitalizations and exacerbations ($P < .001$) (Table 3). QTd value was significantly higher in group 2 compared to group 1 ($P < .001$). There was no difference between the groups according to Tp-e and Tp-e/QTc ($P = .73$; $P = .129$) (Table 1).

DISCUSSION

In this study, we reached 2 important conclusions. The first was that QTc and QTd were significantly higher in GOLD C-D patients compared to GOLD A-B patients. The second

Table 1. Demographic and Clinical Features of the Groups

	Group 1 GOLD A-B	Group 2 GOLD C-D	*P*
Age (years)	62.37 ± 8.82	66.00 ± 9.36	.100
Gender (n %)			
Male	31 (88.57%)	34 (97.14%)	.164
Female	4 (11.43%)	1 (2.86%)	
BMI (kg/m^2)	25.64 ± 3.97	25.54 ± 4.98	.928
Smoking (packs/year)	40.60 ± 21.69	43.03 ± 21.20	.637
mMRC (n %)			
0	6 (17.1%)	2 (5.7%)	.070
1	16 (45.7%)	11 (31.4%)	
2	5 (14.3%)	3 (8.6%)	
3	8 (22.9%)	17 (48.6%)	
4	0 (0%)	2 (5.7%)	
Exacerbation/hospitalizations (n %)			
<2	35 (100%)	0 (0%)	**.001***
>2	0 (0%)	35 (100%)	
ECG parameters			
QTc	412 (400-434)	461 (418-462)	**<.001***
QTd	40 (20-40)	60 (20-80)	**.013***
Tp-e	90 (80-100)	80 (60-110)	.734
Tp-e/QTc	0.22 (0.19-0.24)	0.19 (0.15-0.26)	.129
Pulmonary function tests			
FVC (L)	3.43 (2.29-3.88)	2.42 (2.02-3.29)	**.032***
FVC % predicted	0.90 (0.72-1.00)	0.66 (0.55-0.89)	**.007***
FEV1 (L)	2.08 (1.08-2.43)	1.26 (0.89-1.92)	**.020***
FEV1 % predicted	0.65 ± 0.22	0.50 ± 0.22	**.008***
FEV1/FVC	0.62 (0.54-0.64)	0.54 (0.46-0.62)	**.038***
Laboratory results			
pH	7.42 (7.40-7.43)	7.41 (7.38-7.44)	**.307**
PCO_2 (mmHg)	32.90 ± 4.68	37.17 ± 6.41	**.002***
PO_2 (mmHg)	87.17 ± 16.60	63.26 ± 18.89	**<.001***
SAO_2	97.00 (95.50-97.60)	92.00 (85.80-94.40)	**<.001***

GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; mMRC, Modified British Medical Research Council; QTc, corrected QT interval; QTd, QT dispersion; Tp-e, the peak and the end of the T wave; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SAO_2, oxygen saturation.

Table 2. QTc Positivity-Negativity of the Groups

	QTc					
	Negative		Positive		Total	
	N	%	N	%	N	%
GOLD						
A+B	30	71.4	5	17.9	19.286	***P* < .001***
C+D	12	28.6	23	82.1		

GOLD, Global Initiative for Chronic Obstructive Lung Disease; QTc, corrected QT interval.

was that the remodeling of cardiac repolarization in GOLD C-D patients may be related to the degree of airflow restriction. Remodeling of cardiac repolarization may pose risk for malignant ventricular arrhythmia and sudden cardiac death in these patients.

Chronic obstructive pulmonary disease is associated with increased cardiovascular morbidity and mortality.[2] Previous population-based studies have demonstrated that COPD patients are at 2 to 3 times increased risk of sudden cardiac death.[15] However, the underlying mechanisms of the association between COPD and sudden cardiac death are still unclear, and the reasons behind malignant cardiac arrhythmia and sudden cardiac death in COPD have not been identified. Several factors such as hypoxemia, hypercapnia, acid-base disorders, autonomic dysfunction, and drugs may contribute to arrhythmia development in these patients.

Remodeling of cardiac repolarization is an important mechanism in the development of malignant arrhythmia and sudden cardiac death.[8-10] Measurements obtained from ECG indicate repolarization dispersion and electrical heterogeneity of ventricles during repolarization.[10] Studies have shown an association between measurements showing remodeling of cardiac repolarization, such as in QT interval or [16], QT dispersion, and occurrence of malignant arrhythmia and sudden cardiac death in the cases with cardiac failure,[17] prolonged QT syndrome,[18] and elderly age.[19] Prolonged QT interval and

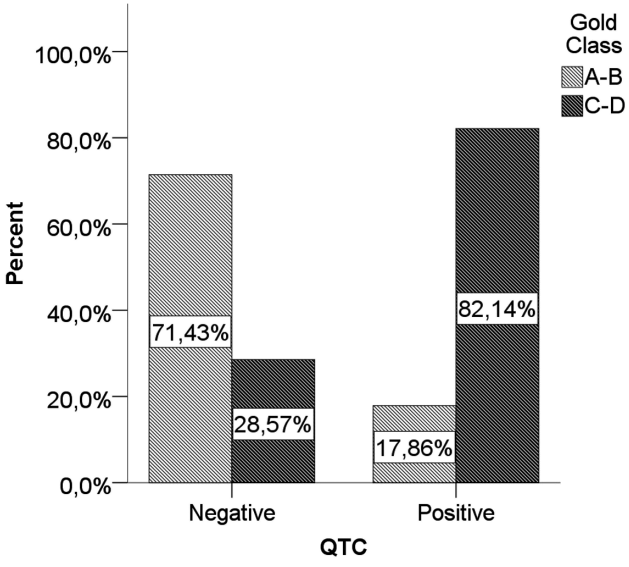

Figure 1. QTc positivity-negativity of the groups.

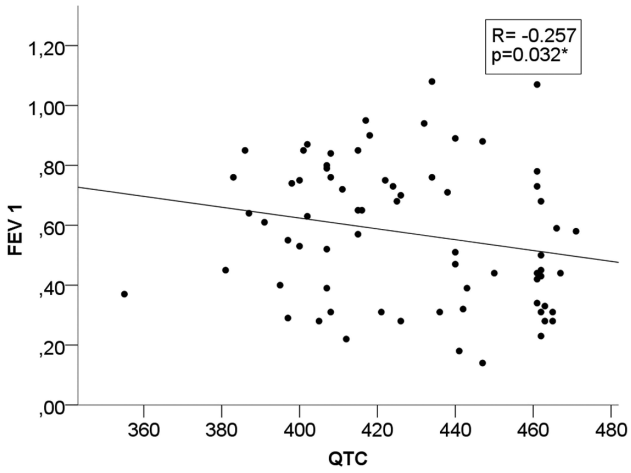

Figure 2. Correlation curve of QTc and FEV_1.

increased QT dispersion are indicators of risk for malignant cardiac arrhythmia and sudden cardiac death.[17,20]

In the sensitivity period of reentrant tachycardia, the QT interval is correlated with ventricular depolarization and repolarization in ECG. Therefore, prolonged QTc of up to >4500 ms has been identified as a risk factor for malignant ventricular arrhythmia and sudden cardiac death.[20,21] QT dispersion reflects spatial differences in myocardial healing time. Previous studies have shown that >60 ms increase in QT dispersion is associated with malignant ventricular arrhythmia[22] and sudden cardiac death.[14] In COPD patients, QT dispersion has been found to correlate with a number of ventricular extrasystoles[23] and a relationship between prolonged QTc interval and sudden cardiac death has been suggested.[24]

Present COPD data is varied due to differences in methodology, diagnostic measures, and analytic approach. Studies have shown that the prevalence of the disease increased in smokers and the elderly, males in developing countries, and equally in both genders or in women in developed countries.[25] In our study, 94.2% of the cases were men and 5.8% were women, while mean age was 64.91 ± 8.74 years in men and 54.80 ± 11.08 years in women. Chronic obstructive pulmonary disease is associated with the risk of cardiac

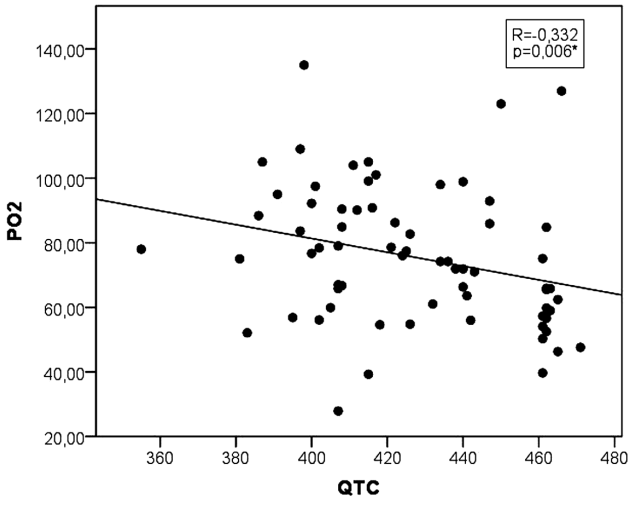

Figure 3. Correlation curve of QTc and P_aO_2.

Table 3. Regression Analysis of QTc

					95% CI OR	
Predictor	**B**	**Wald**	***P***	**OR**	**Lower**	**Upper**
Age	0.011	0.099	.753	1.011	0.946	1.080
Smoking	0.020	1.604	.205	1.020	0.989	1.052
BMI	0.107	2.219	.136	1.113	0.967	1.282
Hospitalizations	−2.282	12.544	**<.001***	0.102	0.029	0.361
mMRC	0.238	0.628	.428	1.268	0.705	2.282

QTc, corrected QT interval; BMI, body mass index; mMRC, Modifiye British Medical Research Council.

arrhythmia. Smoking most likely plays a role in the etiology of both COPD and ischemic cardiac disease. In our study, the smoking history of men and women was mean 40 packs/year.

Some studies have investigated factors which may lead to remodeling changes in cardiac repolarization in COPD patients; however, these studies did not include comorbidities accompanying COPD.[5,22] It is known that about 50% of COPD patients over 50 years of age have coronary artery disease, hypertension, or heart failure which may increase susceptibility to ventricular arrhythmias.[26] In our study, COPD patients without structural heart disease or a history of using cardiac medication were included. These criteria, which limited the number of patients who could be included in the study, were necessary in order to limit the effects of hypoxemia and hypercapnia.

Some evidence points that hypoxemia may prolong repolarization time. Roche et al[27] reported that when healthy subjects were exposed to normobaric hypoxemic conditions, hypoxemia significantly increased QTc interval. Tirlapur et al[7] observed electrocardiographic changes such as prolonged QTc interval in 12 COPD patients with low mean basal SpO_2 (<80%). Sarubbi et al[5] investigated the effects of hypoxemia on QTc dispersion in COPD patients. In the COPD group with hypoxemia, 24-hour oxygen therapy was given, and it was observed that hypoxemia partially resolved and QT dispersion significantly decreased. Their study showed the beneficial effects of correction of hypoxemia and oxygen therapy on lowering increased QT dispersion. It was proposed that hypoxemia affected left ventricular performance, either directly or through sympathetic activity, and that patients with hypoxemic respiratory failure were at increased risk of tachyarrhythmia. Our study investigated how changes in partial oxygen pressure affected QTc value, and it was found that decreased PaO_2 caused an increase in QTc. These findings indicated that changes in blood gas levels may cause increased QTd in COPD patients. Contrary to these studies, Smith et al[28] conducted research on 20 COPD patients and compared groups with desaturation (<90%) and normal saturation, and ischemic ECG changes were not observed in any patient during exercise. No changes in QTc dispersion were observed before or after exercise either. Furthermore, receiving oxygen therapy before and after the test had not affected the QTc value. The aforementioned study did not find any evidence that exercise increased or exacerbated hypoxemia-induced QTc dispersion.[28]

Evidence from long-term studies indicates that decreased FEV1 is associated with an increased risk of ischemic heart failure, cerebral disease, and sudden cardiac death, even after conventional cardiovascular risk factors were eliminated.[29,30] High prevalence of cardiac arrhythmia and severity of airflow obstruction are thought to be associated with the occurrence of arrhythmia in COPD patients.[31,32] In our study, FEV1, FVC, and FEV1/FVC values were significantly lower in the GOLD C-D group compared to the GOLD A-B group, and there was a statistically significant negative correlation between FEV1 and QTc. As the restricted airflow of the cases increased, an increase in QTc values was observed. Contrary to our findings, Tug et al[33] assessed 35 COPD patients who were classified as mild or moderate-severe COPD and found that there was no difference between mild and moderate-severe cases in terms of QT interval or QTc. In a study by Zulli et al.[34] a single-variable analysis of 246 COPD patients without comorbidity showed that FEV1 and FVC were associated with QT dispersion; however, multivariate analysis did not yield a significant correlation. Yildiz et al[22] conducted a small-scale case–control study on COPD patients, in which ventricular arrhythmia was significantly correlated with increased QT dispersion but not with pulmonary function tests, hypoxemia, or degree of hypercapnia. In addition, there was a correlation between the parasympathetic component of heart rate variability and QT dispersion, and it was suggested that autonomic dysfunction may play a role in the development of arrhythmia in these patients.[22]

There is also evidence that autonomic neuropathy may lead to prolonged cardiac repolarization in COPD. Stewart et al[24] compared 17 COPD patients with autonomic neuropathy to 17 COPD patients without autonomic neuropathy and found that QTc measures were significantly longer in those with autonomic neuropathy. They concluded that autonomic neuropathy may also extend QTc.[24] However, our study did not assess autonomic neuropathy, and therefore, our results cannot be directly compared with the results of the aforementioned study.

Our study had some limitations. Standard 12-derivation ECG was used and 24-hour continuous ECG was not conducted. Therefore, it was impossible to evaluate the causal relationship between remodeling of cardiac repolarization, malignant ventricular arrhythmia, and sudden cardiac death. It is currently unknown whether or not prolonged cardiac repolarization induced sudden cardiac death in patients with

COPD. In order to understand whether or not prolonged cardiac repolarization causes malignant ventricular arrhythmia or sudden cardiac death, further controlled longitudinal studies are warranted.

In conclusion, QTc and QTd are noninvasive indicators of arrhythmogenicity, and our findings demonstrate that QTc and QTd are associated factors in COPD. Increased dispersion of repolarization and remodeling of cardiac repolarization in the COPD population may be related to hypoxemia and airflow obstruction. Remodeling of cardiac repolarization may expose an increased risk of malignant ventricular arrhythmia and cardiac death.

CONCLUSION

Chronic obstructive pulmonary disease is a widespread crippling disease and the fourth leading cause of death after ischemic heart disease. Comorbidities are prevalent in COPD and are significant in that they have negative effects on the person's health condition. Increased risk of cardiac arrhythmia and sudden cardiac death are known to be associated with COPD. Cardiac repolarization remodeling may put these patients at high risk for malignant ventricular arrhythmia and sudden cardiac death. Therefore, ECG indicators of repolarization may be important in identifying COPD patients at high risk of developing cardiac arrhythmia.

Ethics Committee Approval: The study was approved by the ethics committee of Sutcu Imam University Faculty of Medicine (Feb 14, 2018; (Approval No:05).

Informed Consent: Written informed consent was obtained from each participant who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Design - F.B.; Resources -F.B., F.A.U.; Materials - F.A.U, F.B., E.A.; Data Collection and/or Processing - F.A.U., F.B.; E.A., N.A., H.K., Analysis and/or Interpretation - F.B., F.A.U., A.D.,; Literature Review - F.B., F.A.U.; Writing – F.B., F.A.U.; Critical Review - F.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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