ARE THE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE A RISK FACTOR FOR CARDIAC ARRHYTHMIA?

Kronik Obstrüktif Akciğer Hastalığı Alevlenmeleri Kardiyak Aritmi İçin Risk Faktörü müdür?

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ABSTRACT

Objective: Hypoxemia, hypercapnia, and increased automaticity during exacerbations contribute to abnormal atrial and ventricular repolarization in chronic obstructive pulmonary disease (COPD), raising the risk of arrhythmias. This study aimed to predict the likelihood of arrhythmias by analyzing electrocardiograms (ECGs) of patients experiencing COPD attacks.

Material and Methods: A total of 120 patients (66 in the COPD group and 54 in the control group) were included. Statistical analysis compared QT and QTc interval maximum (max), minimum (min), and dispersion (disp); T-wave peak to end (Tp-e) max, min, and disp; Tp-e max/QT max, Tp-e max/QTc max ratios; and P wave max, min, and disp durations among patients.

Results: Of the males in the study, 48 (64%) were in the COPD group and 27 (36%) in the control group, while 18 (40%) of the females were in the COPD group and 27 (60%) in the control group. There were no significant differences in patient ages or levels of sodium and potassium ($p = 0.189$, 0.353, and 0.071). Significant differences were found in QT max and min between groups, while QT disp showed no significant difference ($p < 0.001$, $p < 0.001$, and $p = 0.490$). Tp-e max, min, and disp values differed significantly between the COPD and control groups ($p = 0.041$, $p < 0.001$, and $p = 0.001$, respectively). No significant difference was observed between groups in terms of P max duration ($p = 0.442$), but significant differences were found in P min and disp durations ($p = 0.003$ and $p < 0.001$, respectively). Receiver operating characteristic analysis identified 30 ms as the cutoff for both P disp and Tp-e disp values, showing a significant difference.

Conclusion: This study is the first to detect increased dispersions of P wave and Tp-e intervals (without an increase in QTc disp.) during the evaluation of atrial and ventricular arrhythmia risks during COPD acute attacks.

Keywords: *Chronic Obstructive Pulmonary Disease; Electrocardiography; Arrhythmia*

ÖZET

Amaç: Kronik Obstrüktif Akciğer Hastalığı (KOAH) olan hastalarda hipoksemi, hiperkapni ve otomatisite ile artan aritmi riskini, KOAH ataklarını geçiren hastaların elektrokardiyogramlarını (EKG) değerlendirerek öngörmeyi amaçladık.

Gereç ve Yöntemler: Toplamda 120 hasta (KOAH grubunda 66 ve kontrol grubunda 54 hasta) dahil edildi. İki grup arasındaki farklar, hastaların EKG parametrelerinde (milisaniye cinsinden) QT ve QTc aralığı maksimum (max), minimum (min) ve dispersiyon (disp); T dalga pikten sona (Tp-e) max, min ve disp; Tp-e max/QT max, Tp-e max/QTc max oranları; ve P dalgası max, min ve disp süresini belirleyerek istatistiksel olarak incelendi.

Bulgular: Çalışmaya dahil edilen erkeklerin 48'i (%64) KOAH grubundaydı ve 27'si (%36) kontrol grubundaydı, kadınların 18'i (%40) KOAH grubundayken 27'si (%60) kontrol grubundaydı. Hastaların yaşları ile sodyum ve potasyum seviyeleri arasında anlamlı bir fark bulunmadı (sırasıyla $p = 0,189$, 0,353 ve 0,071). Gruplar arasında QT max ve min arasında anlamlı bir fark bulunurken, QT disp açısından fark bulunmadı (sırasıyla $p < 0,001$, $p < 0,001$ ve $p = 0,490$). KOAH ve kontrol grupları arasında Tp-e max, min ve disp değerleri arasında anlamlı bir fark bulunmaktaydı (sırasıyla $p = 0,041$, $p < 0,001$ ve $p = 0,001$). Gruplar arasında P max süresi açısından anlamlı bir fark bulunmazken ($p = 0,442$), P min ve disp süreleri arasında anlamlı farklar belirlendi (sırasıyla $p = 0,003$ ve $p < 0,001$). P disp ve Tp-e disp değerleri için yapılan ROC analizinde, her iki parametre için de kesim değeri olarak 30 ms belirlendi.

Sonuç: Bilgilerimize göre, P dalga ve Tp-e aralıklarının dispersiyonlarının (QTc disp artışı olmaksızın) yükseldiği ve KOAH akut ataklarındaki atriyal ve ventriküler aritmia riskinin değerlendirilmesinde farklılık olduğu ilk çalışma olduğu görülmektedir.

Anahtar Kelimeler: *Kronik Obstrüktif Akciğer Hastalığı; Elektrokardiyografi; Aritmi*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge, contributing substantially to morbidity, mortality, and economic strain. In 2016 alone, it accounted for nearly three million deaths, constituting approximately 5.4% of all global fatalities (1). This figure surpasses deaths from sudden cardiac arrest in the general population by two to three times when mortality causes are analyzed within this demographic (2). Studies indicate that cardiac repolarization abnormalities and increased dispersion among COPD patients lead to malignant ventricular arrhythmias and sudden cardiac deaths (3,4). Longitudinal observations of COPD patients reveal various pathophysiological mechanisms such as heightened ventricular afterload, right ventricular hypertrophy, and structural alterations associated with emphysema, all of which contribute to electrocardiographic (ECG) alterations (5). Additionally, existing research underscores a heightened risk of arrhythmias during acute COPD exacerbations (6,7). These arrhythmias often stem from abnormal atrial and ventricular repolarization due to increased automaticity, typically occurring during exacerbations characterized by changes in oxygen, carbon dioxide, and pH levels (8,9).

Detecting ECG changes in patients experiencing acute exacerbations of COPD can significantly impact patient outcomes. It's crucial to consider that COPD exacerbations may also disrupt cardiac rhythm.

In this study, our objective is to predict the likelihood of arrhythmias by comparing ECG changes among patients admitted to the emergency department for acute COPD exacerbations.

MATERIALS AND METHODS

Patients presenting with dyspnea and diagnosed with acute COPD exacerbation at a tertiary emergency department between January 1, 2019, and June 30, 2019, were included in this study. A total of 709 patients identified with dyspnea code R06.0 according to the tenth revision of the International Classification of Diseases were retrospectively analyzed. Among these, 536 patients without prior COPD follow-up were excluded, leaving 173 patients whose emergency service records were reviewed. Twenty-two patients with unavailable ECG records and 85 patients exhibiting ECG artifacts or arrhythmias were further excluded, resulting in the inclusion of 66 patients with evaluable acute data (Figure 1). Additionally, 54 individuals without respiratory complaints or diagnosed cardiac pathology (who underwent ECG for exclusion purposes) during the same period were included as the control group. Demographic characteristics (age and gender), ECG parameters (P wave, QT interval, and T wave peak–end duration [Tp-e]), and electrolyte levels (sodium and potassium) of the study groups were analyzed. The study was approved by the Kütahya Health Sciences University Noninvasive Ethnic Group (March 17, 2021/05-12). Routine treatment data for COPD and control groups were retrieved from the hospital information management system and patient records, with no additional voluntary consent obtained from patients or their families.

In ECG evaluation, 12-lead ECGs captured via smartphones and uploaded to computers were interpreted by an experienced emergency medicine physician (Figure 2). ECG recordings of all patients were obtained using a MAC 800 ECG machine (2017) device at a speed of 25 mm/s and amplitude of 10 mm/mV. Maximum (max) duration in the longest lead and minimum (min) in the shortest lead were calculated for ECG parameters, with dispersion (disp) durations determined by their difference. The QT interval, from the beginning of the QRS complex to the end of the T wave, was measured. Correction of QT (QTc) interval using the Bazett formula was calculated. Tp-e, the distance between T wave peak (Tp) and isoelectric line or last endpoint, was determined using the tangent method (10). QT max, QT min, QT disp, QTc max, QTc min, QTc disp, Tp-e max, Tp-e min, Tp-e disp, P max, P min, and P disp were calculated. Tp-e/QT and Tp-e/QTc ratios were included in the dataset.

Statistical Analysis

SPSS v.20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was utilized for statistical analysis. Normality was tested using the Kolmogorov–Smirnov test. Normally distributed numeric variables were expressed as mean ± standard deviation (SD), non-normally distributed variables as median (interquartile range [IQR]), and

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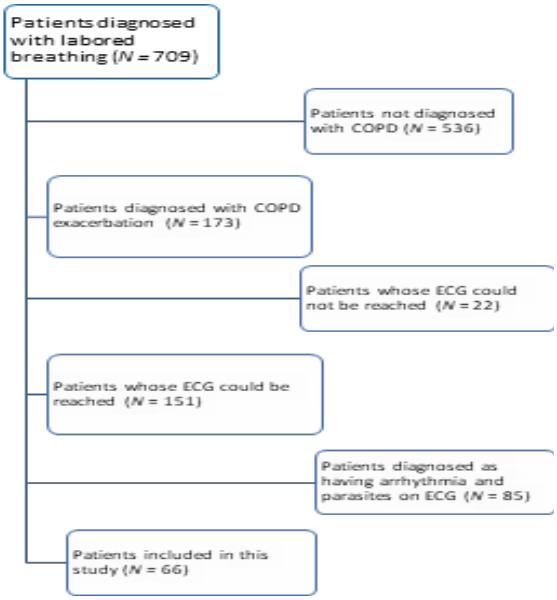

Figure 1. Flowchart of the patients selected for this study.

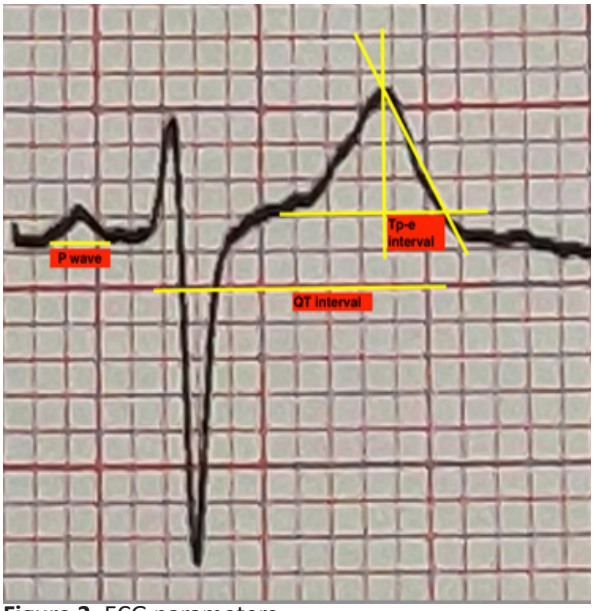

Figure 2. ECG parameters.

categorical variables as frequencies and percentages. Student's t-test and Mann-Whitney U test were used for normally and non-normally distributed numeric variables, respectively. Chi-squared or Fisher exact test was employed for categorical variables. Receiver operating characteristic (ROC) analysis was conducted for variables with significant between-group differences. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated using the Youden Index cutoff. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 120 patients participated in the study, with 66 in the COPD group and 54 in the control group. Among the participants, 48 (64%) males were in the COPD group and 27 (60%) in the control group, while 18 (40%) females were in the COPD group and 27 (60%) in the control group. COPD was more prevalent in males than in females across the study groups (p = 0.011). The mean age in the COPD group was 68.5 years, while it was 66.5 years in the control group, with no significant difference observed between the two groups (p = 0.189). Regarding electrolyte parameters, the mean sodium levels in the COPD and control groups were 140 mmol/L and 140 mmol/L, respectively, and the mean potassium levels were 4.1 mmol/L and 4.2 mmol/L, respectively. No statistically significant differences were found in the electrolyte values between the two groups (p = 0.353, p = 0.071). Detailed results are presented in Table 1.

ECG parameters were assessed in milliseconds (ms). In both the control and study groups, the median QT max was 360 ms and 400 ms, QT min was 300 ms and 320 ms, and QT disp was 40 ms and 40 ms, respectively. While there was a significant difference between QT max and min values, no statistically significant difference was observed in terms of QT disp (p < 0.001, p < 0.001, and p = 0.490). The mean (±SD) QTc max duration in the control and study groups was 439.9 ± 32.11 and 449.9 ± 37.52 ms, respectively, and QTc min was 377.8 ± 30.25 and 380.7 ± 31.18 ms, respectively, with no statistically significant difference detected between the two groups (p = 0.122 and p = 0.595). QTc disp was measured as 54.5 ms in the study group and 51.0 ms in the control group, with no significant difference between the groups (p = 0.820).

The median Tp-e max, min, and disp durations in the study and control groups were as follows: 80ms-80ms, 50ms-60ms, and 40ms-20ms, respectively, with a statistically significant difference between the groups

(p = 0.041, p < 0.001, and p = 0.001). The median P max, P min, and P disp were 100ms, 60ms, 40ms in the study group and 80ms, 60ms, 20ms in the control group, respectively. While there was no difference in P max between the groups (p = 0.445), there was a statistically significant difference in P min and disp (p < 0.001 and p < 0.001). Detailed results are provided in Table 2.

Cutoff values were determined via ROC analysis for P disp and Tp-e disp, which exhibited significant differences between groups. The Area under the curve (AUC) values were 0.712 and 0.671, respectively (Figure 3). According to the highest Youden Index, the determined cutoff value was evaluated as 30 ms. According to the four-cell chart based on this, sensitivity values were 87.88% and 80.3%, and specificity values were 55.56% and 61.11% for P disp and Tp-e disp, respectively. The PPV, NPV, LR+, and LR− values (calculated using the data from the four-cell chart on the website https://www.aciltipakademisi.org/istatistik-hesaplama-araclari/) for P disp were 70.73%, 78.95%, 1.98, and 0.22, respectively, and for Tp-e disp were 71.62%, 71.74%, 2.06, and 0.32, respectively (Table 3).

Tablo 1. General characteristics and electrolyte values

		Control group (*N* = 54)	COPD group (*N* = 66)	*p*
Age (year)[a]		66.5, 14 (40–82)	68.5, 18 (38–95)	0.189*
Gender	Men	27 (36%)	48 (64%)	0.011**
	Women	27 (60%)	18 (40%)	
Sodium (mmol/L)[a]		140, 3 (129–143)	140, 5 (126–146)	0.353*
Potassium (mmol/L)[a]		4.20, 0.58 (3.30–6.30)	4.10, 0.90 (2.70–6.10)	0.071*

* Mann–Whitney U-test; ** Chi-squared test. IQR: Interquartile Range, COPD: chronic obstructive pulmonary disease
a: Median, IQR (min-max)

Tablo 2. Comparison of ECG parameters of the two groups.

ECG parameters (ms)	Control group (*N* = 54)	COPD group (*N* = 66)	*p*
QT max[a]	400.45 (320–480)	360.60 (280–520)	**<0.001***
QT min[a]	320.40 (280–400)	300.40 (240–440)	**<0.001***
QT disp[a]	40.40 (0–140)	40.20 (20–120)	0.490*
QTc max[b]	449.9 ± 37.52	439.9 ± 32.11	0.122**
QTc min[b]	380.7 ± 31.18	377.8 ± 30.25	0.595**
QTc disp[a]	51.49 (0–153)	55.30 (26–134)	0.820*
Tp-e max[a]	80.40 (40–160)	80.20 (50–120)	**0.041***
Tp-e min[a]	60.20 (40–100)	50.20 (30–80)	**<0.001***
Tp-e disp[a]	20.40 (0–80)	40.10 (20–80)	**0.001***
Tp-e /QT[a]	0.240, 0.05 (0.12–0.38)	0.250, 0.04 (0.15–0.33)	0.615*
Tp-e/QTc [a]	0.190, 0.080 (0.11–0.34)	0.189, 0.054 (0.11–0.27)	0.301*
P max[a]	80.40 (40–200)	100.20 (50–160)	0.445*
P min[a]	60.40 (40–80)	60.20 (30–80)	**<0.001***
P disp[a]	20.20 (0–140)	40.13 (10–100)	**<0.001***

* Mann–Whitney U-test; ** Student's t-test. Bold p values are statistically significant. IQR: Interquartile Range, SD: Standard deviation, COPD: chronic obstructive pulmonary disease a: Median, IQR (min-max) b: Mean ± SD Tp-e: T wave peak–end duration, QTc: corrected QT interval duration, max: maximum, min: minimum, disp: dispersion

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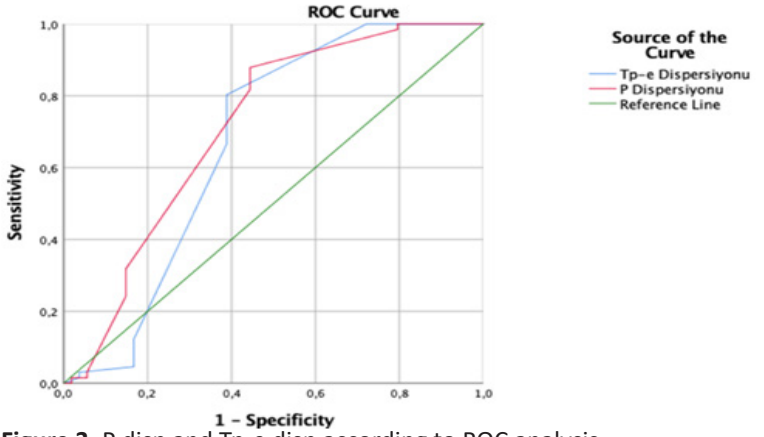

Figure 3. P disp and Tp-e disp according to ROC analysis.

Tablo 3. Diagnostic sensitivity tests for P Wave and Tp-e dispersion according to ROC analysis.

	Cutoff (ms)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR–	Youden Index	AUC
P dispersion	30	87.88	55.56	70.73	78.95	1.98	0.22	0.434	0.712
Tp-e dispersion	30	80.3	61.11	71.62	71.74	2.06	0.32	0.414	0.671

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-:negative likelihood ratio, AUC: Area Under Curve, Tp-e: T wave peak–end

DISCUSSION

COPD stands out as a major cause of mortality and morbidity (11). While predominantly observed in male smokers, its prevalence is increasing among females (12). Ntritsos et al.'s systematic review and meta-analysis in 2018 reported a higher prevalence of COPD in males than females, with the gender gap diminishing around the age of 40. In urban areas, the prevalence was 13.03% in males and 8.34% in females, while in rural areas, it was 10.69% in males and 5.96% in females (13). In our study, COPD was more prevalent in males than females ($p = 0.011$). Although there was no statistically significant difference in mean ages between the study and control groups ($p = 0.189$), COPD incidence rates were higher in older patients.

Electrolyte imbalances, particularly potassium, calcium, and magnesium, have proarrhythmic effects by altering cardiac ionic flow kinetics, with sodium playing a lesser role (14). While Ogan N et al. observed differences in K and Na electrolytes between study and control groups, mean values in both groups fell within the normal range. No significant differences were found in sodium and potassium levels between the groups ($p = 0.353$ and $p = 0.071$), consistent with previous studies. COPD carries an increased risk of cardiovascular diseases such as conduction abnormalities, arrhythmias, and ischemic heart disease. ECG abnormalities in COPD patients, including fatal arrhythmias, contribute to increased mortality rates (16, 17). Atrial fibrillation, multifocal atrial tachycardia, and ventricular arrhythmias are common in COPD patients (18). Risk factors such as inhaled bronchodilators, age, smoking, hypoxemia, and respiratory acidosis contribute to arrhythmias (19). In our study, we evaluated ECG parameters comprehensively to predict both atrial and ventricular arrhythmias in COPD patients. The QT interval, reflecting ventricular depolarization and repolarization, requires correction for heart rate to compare with reference values due to its heart rate dependence (20). While significant differences were observed between COPD and control groups in terms of QT max and min values ($p < 0.001$ and $p < 0.001$), no difference was found in QT disp ($p = 0.490$). Similarly, there were no differences in QTc max, min, and disp between the groups ($p = 0.122$, $p = 0.595$, and $p = 0.820$). Although Sarubbi et al. reported differences in QTc

disp, their study population was younger, suggesting age-related differences (21). These ECG parameters were not predictive of patient hospitalization, thus not definitive markers (21). Sievi et al. reported similar average QTc values in COPD patients (437.9 ± 29.5) to our study (439.9 ± 32.11) (2). The lack of differences between our study's control and treatment groups may be attributed to the similar ages and presence of other chronic diseases in the control group.

Tp-e duration has been studied as a marker for repolarization abnormalities and T wave arrhythmias in various conditions, including hypertension, ischemic heart disease, Brugada syndrome, Chagas disease, and pulmonary embolism (22). While there is no literature predicting Tp-e duration and arrhythmias specifically in COPD patients, Tasolar et al. found higher Tp-e, corrected Tp-e, and Tp-e/QTc ratios in smokers compared to nonsmokers (27). Consistent with this, our study found significant differences in Tp-e max, min, and disp between COPD and control groups ($p = 0.041$, $p < 0.001$, and $p = 0.001$), suggesting Tp-e duration could predict ventricular arrhythmias. Bhatt SP et al.state that P-wave dispersion is higher during the acute phase compared to the stable phase, and tends to be greater in patients experiencing more frequent exacerbations. (29). Also, our study found a significant difference in P disp between the groups, possibly due to unstable ECG evaluations during COPD attacks. Similarly, Cimci et al. reported increased wave dispersion in the COPD group compared to controls (30). Cutoff values determined by ROC analysis for P disp and Tp-e disp, which differed significantly between groups, were both 30 ms. While AUC values were not high, LR− values were meaningful. Our study provides a basis for future prospective studies due to the limited research in this area.

Limitations include the control group's similar age to the treatment group and lack of consideration for chronic diseases in controls besides COPD. Despite manual measurement in a digital environment, microscopic ECG evaluation was not performed. Small sample size and retrospective design are additional limitations. Prospective cohort studies are necessary to explore these findings further and evaluate arrhythmia development in COPD patients.

CONCLUSION

To the best of our knowledge, this study is the first to identify an increase in the dispersions of P-wave and Tp-e intervals (without an increase in QTc dispersion) during the evaluation of atrial and ventricular arrhythmia risks in COPD acute attacks. It is imperative for doctors in the emergency service, where treatment for COPD attacks is administered, to conduct a detailed ECG evaluation of these patients to enable early diagnosis of arrhythmia-related mortality.

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