ORIGINAL ARTICLE

The relationship between systolic pulmonary arterial pressure and Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in patients with newly diagnosed chronic obstructive pulmonary disease

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Abstract

Introduction: The risk of sudden cardiac death (SCD) and arrhythmias has been shown to be common in chronic obstructive pulmonary disease (COPD) subjects. We aimed to evaluate the markers of arrhythmia such as QT, QTc (corrected QT), Tp-e, and cTp-e (corrected Tp-e) intervals, Tp-e/QT ratio, and Tp-e/QTc ratio in newly diagnosed COPD subjects in both right and left precordial leads.

Materials and Methods: The study group consisted of 74 subjects with obstructive respiratory function tests (RFTs). The control group consisted of 78 subjects who had nonobstructive RFTs. RFTs, electrocardiograms (ECG), and transthoracic echocardiograms (TTE) were performed, and QTR (QT interval in right precordial leads), QTL (QT interval in left precordial leads), Tp-eR (Tp-e interval in right precordial leads), and Tp-eL (Tp-e interval in left precordial leads) intervals; systolic pulmonary arterial pressure (sPAP); forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC); and peripheral oxygen saturation (POS) values were measured.

Results: Tp-eR interval 85.82 ± 5.34 millisecond (ms) versus 62.87 ± 3.55 ms ($t = 31.29/p < .00001$), cTp-eR interval 97.51 ± 7.18 ms versus 71.07 ± 4.58 ms ($t = 27.20/p < .00001$), Tp-eR/QTR ratio 0.234 ± 0.02 versus 0.164 ± 0.01 ($t = 2.2/p = .014$), and Tp-eR/QTcR ratio 0.201 ± 0.01 versus 0.141 ± 0.01 ($t = 1.92/p = .028$) were statistically significantly higher in COPD subjects. There was a strong negative correlation between RFT and sPAP (sPAP, 29.93 ± 5.1 mm Hg; and FEV₁/FVC, $63.78 \pm 3.33\%$, $r = -.85/p < .00001$). There was a moderate positive correlation between sPAP and Tp-eR.

Conclusion: We found Tp-e and cTp-e intervals, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in the COPD patients than in the control group. In addition, in the COPD group, heart rate variability (HRV) parameters were significantly lower on ECG.

KEYWORDS

chronic obstructive pulmonary disease, respiratory function test, systolic pulmonary arterial pressure, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio

1 | INTRODUCTION

COPD not only affects the lungs but also affects the heart and the other organs (Barnes & Celli, 2009). Both the right and left sides of

the heart are affected in COPD (Zulli et al., 2006). COPD may have systemic effects not only due to increased pulmonary arterial pressure but also by the release of inflammatory mediators (Decramer et al., 2008). Secreted low-intensity inflammatory mediators may cause

oxidative stress and endothelial dysfunction, which can lead to heart disease, which is the most common cause of morbidity and mortality in COPD (Eickhoff et al., 2008).

Large-scale studies have shown that sudden cardiac death rate in COPD subjects was 2–3 times higher than in the healthy population. In particular, this rate increases as age increases. The risk of SCD especially increases after acute exacerbation (Karoli & Rebrov, 2017). The most important mechanism of SCD is ventricular arrhythmias. These arrhythmias can also occur without significant cardiac disease. Asystole, ventricular tachycardia, and fibrillation are the causes of SCD (Dalia et al., 2019). Disorders of cardiac autonomic modulation have been found in subjects with COPD, especially in subjects with hypoxemia. These disorders are characterized by a higher heart rate at rest, a decrease in baroreflex sensitivity, a reduction in heart rate variability, and heart rate recovery disorder (Van Gestel & Steier, 2010).

Several predictors for ventricular arrhythmias have been investigated. Some of these are reduced circadian heart rate, QT dispersion, QT prolongation, microvolt T-wave alternans, and late atrial and ventricular potentials (Syromyatnikova et al., 2016; Verrier et al., 2011). The most emphasized one of these was QT prolongation (Van den Berg, Stricker, Brusselle, & Lahousse, 2016).

Recently, the T peak-end interval (Tp-e interval) has been emphasized among the predictors of malignant ventricular arrhythmias. The time between the peak and the end of the T wave (Tp-e interval) is accepted as an index of transmural dispersion of ventricular repolarization (Kors, Ritsema van Eck, & van Herpen, 2008). Tp-e/QT and Tp-e/QTc ratios are also used as electrocardiographic indexes of ventricular arrhythmogenesis (Gupta et al., 2008).

It is emphasized that the Tp-e interval is prolonged in many diseases, and it is related to malignant ventricular arrhythmias and SCD (Cekirdekci & Bugan, 2018; Kahraman et al., 2018; Wang, Zhang, Gao, Wu, & Zhu, 2019). However, Tp-eR (Tp-e interval in the right precordial leads) interval, Tp-eR/QT ratio (QT interval in the right precordial leads), and Tp-eR/QTcR (corrected QT interval in the right precordial leads) ratio have not been evaluated in subjects with newly diagnosed COPD, so far. Our study aims to investigate the Tp-eR interval, Tp-eR/QT ratio, and Tp-eR/QTcR ratio in newly diagnosed COPD subjects and to observe how they are affected at the onset of the COPD in this subject group.

2 | MATERIALS AND METHODS

2.1 | Study population

Between August 2017 and December 2018, 74 subjects (41 male, 55.40% and 33 female, 44.60%) who presented to the outpatient clinic of chest disease with dyspnea and detected obstruction in pulmonary function test were included in the study. The detection of forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] <70% was accepted as an obstructive finding (Vogelmeier et al., 2017). The mean age of this group was 55.7 ± 13.6 years. The control group consisted of 78 subjects (45 male, 57.69% and 33 female,

42.31%) with a normal pulmonary function test. The mean age of the control group was 57.3 ± 12.4 years. The exclusion criteria were previous diagnosis of COPD and receiving bronchodilator therapy, having any systemic disease such as diabetes mellitus or hypertension, having impaired liver or kidney function test, having electrolyte imbalance in routine blood examination, having anemia or thyroid dysfunction, having a disease that may affect the heart, having coronary arterial disease, the presence of a cardiac pacemaker, having diagnosis of cancer, taking any cardiac treatment, the subjects whose tricuspid insufficiency is not enough to calculate sPAP and the subjects who have more than the mild degree of tricuspid insufficiency, having large right chambers in the heart, and being unable to perform pulmonary function test. Informed consent was obtained from each subject. There was no statistically significant difference between the demographic characteristics of the study and control groups (Table 1). Subjects are questioned in terms of demographic information, smoking habits, and other diseases. After a full physical examination, including measurement of blood pressure three times after five minutes of rest, the study and control groups were taken to RFT, ECG, TTE, and pulse oximetry. Besides, the pulse oximetry values of the study and control groups were measured during the rest.

2.2 | Respiratory function test (RFT)

The study group was taken to the RFT in a sitting position after 5 min of rest. After deep inspiration, the subject was asked to perform the expiration vigorously to the spirometer, after deep inspiration. The same procedure was performed three times successively. The values obtained from these three measurements were determined using averages. Subjects with FEV_1/FVC ratio of <70% were considered to have obstructive findings (Vogelmeier et al., 2017) and were included in the study. Subjects who could not make enough expiration were excluded from the study.

2.3 | Pulse oximetry

Peripheral oxygen saturation (POS) of the subjects was measured by pulse oximetry. The measurements were taken under normal weather conditions when the subjects were in the supine position and after 5 min of rest. During a one-minute pulse oximetry measurement, the most common value was recorded in the display. POS was indicated as %.

2.4 | Electrocardiography (ECG)

The standard 12-lead and right precordial lead ($V_{1-6}R$) ECG recordings were obtained at the supine position with paper at a speed of 25 mm/sec and 10 mm/mV amplitude by using standard ECG system (Cardiofax V model 9320; Nihon Kohden). ECG length was 10 s; therefore, depending on the heart rate, there were 4–6 beats per lead. ECGs were measured manually by the use of a magnifying glass (TorQ, 150 mm Digital Caliper LCD) by two blinded cardiologists having no information about the subjects. The RR interval,

TABLE 1 Statistical comparison of the values of the study and the control groups

Variables	Study group (n = 74)	Control group (n = 78)	p Values
Age, year	55.70 ± 13.60	57.30 ± 12.40	.16
Blood pressure, mm Hg	123.40 ± 13.60	119.40 ± 12.80	.054
Men, %	55.40	57.69	.77
Women, %	44.60	42.31	.77
BMI, kg/m ²	27.40 ± 2.41	28.10 ± 3.40	.075
Basal HR, beats/minute	77.68 ± 6.52	77.25 ± 5.29	.32
POS, %	88.55 ± 2.45	95.46 ± 2.11	<.01
RFT, %	63.78 ± 3.33	85.397 ± 3.18	<.01
sPAP, mm Hg	29.93 ± 5.10	20.24 ± 2.99	<.01
Tp-eR interval, ms	85.82 ± 5.34	62.87 ± 3.55	<.01
cTp-eR interval, ms	97.51 ± 7.18	71.07 ± 4.58	<.01
Tp-eL interval, ms	73.86 ± 4.19	73.80 ± 3.88	.46
cTp-eL interval, ms	83.98 ± 6.09	83.69 ± 5.23	.37
QTR interval, ms	377.85 ± 15.77	363.81 ± 14.65	<.01
QTcR interval, ms	431.91 ± 19.22	415.46 ± 17.43	<.01
QTL interval, ms	391.81 ± 16.61	390.76 ± 16.28	.35
QTcL interval, ms	446.37 ± 17.43	444.57 ± 18.39	.24
Tp-eR/QTR ratio	0.234 ± 0.02	0.164 ± 0.01	.01
Tp-eR/QTcR ratio	0.201 ± 0.01	0.141 ± 0.01	.02
Tp-eL/QTL ratio	0.189 ± 0.01	0.188 ± 0.01	.48
Tp-eL/QTcL ratio	0.165 ± 0.01	0.166 ± 0.01	.48
Maximum NN interval, ms	819.53 ± 33.25	867.37 ± 46.26	<.01
Minimum NN interval, ms	735.84 ± 29.53	684.48 ± 27.36	<.01
Number of NN in ECG	30.06 ± 1.95	29.45 ± 2.11	.06
Mean NN interval, ms	773.39 ± 35.45	775.70 ± 44.47	.69
SDNN in ECG, ms	35.45 ± 14.25	45.47 ± 19.56	<.01
Number of NN50 in ECG	1.02 ± 0.34	2.58 ± 0.57	<.01
pNN50 in ECG, %	3.31 ± 2.17	8.76 ± 5.32	<.01
RMSSD in ECG, ms	20.81 ± 8.46	27.46 ± 9.52	<.01

Abbreviations: cTp-eL, corrected Tp-e interval in the left precordial leads; cTp-eR, corrected Tp-e interval in the right precordial leads; HR, heart rate; pNN50, the ratio of the number of NN intervals' difference greater than 50 ms to all NN intervals in ECG; POS, peripheral oxygen saturation; QTcL, corrected QT interval in the left precordial leads; QTcR, corrected QT interval in the right precordial leads; QTL, QT interval in the left precordial leads; QTR, QT interval in the right precordial leads; RFT, respiratory function test; RMSSD, standard deviation of root mean square of all NN intervals in ECG; SDNN, standard deviation of average of all NN intervals in ECG; sNN50, number of NN intervals' difference greater than 50 ms; sPAP, systolic pulmonary arterial pressure; Tp-eL, Tp-e interval in the left precordial leads; Tp-eR, Tp-e interval in the right precordial leads.

Bold values indicate *P*-value < .05

QT interval, and T peak-end interval of the ECG recordings were measured manually with an accuracy of 0.01 mm. In addition to left precordial leads, according to Boston Scientific ECG screening tools, right ventricular precordial leads were taken by using the vertical mirror image of the left ventricular precordial leads and displacement of right and left extremity electrodes (Curry et al., 2018). Left fourth intercostal space of sternum side (1 cm) was used as V₁R, right fourth intercostal space of sternum side (1 cm) was used as V₂R, right fifth intercostal space and right midclavicular line intersection was used as V₄R, midpoint of V₄R-V₂R line was used as V₃R, intersection point of right front axillary line and fifth intercostal space was used as V₅R, and intersection point of right middle

axillary line and right fifth intercostal space was used as V₆R. The RR interval was taken as the time from the peak of an R wave to the peak point of the other R wave. This measurement was calculated between at least in three precordial leads and at least three consecutive R waves for Tp-e interval in both right and left precordial leads (V₂₋₅ precordial right and left leads). The end of the QT interval was termed as the point where the T wave returned to the isoelectric line from the onset of the QRS wave. This measurement was calculated at least both in three right and left precordial leads (V₂₋₅ precordial right and left leads) and in three consecutive QRS waves in one lead for QT interval. The data of ECG with papers at a speed of 25 mm/sec amplitude of 10 mm/mV, measured in mm with the

digital caliper, were calculated as millisecond multiplied by 40. QTc was calculated using the Bazett formula. T peak-end interval was calculated by including the T wave from the peak to baseline in the $V_{2-5}R$ and $V_{2-5}L$ leads. Tp-e intervals were calculated by multiplying the obtained value in milliseconds by 40. If the U wave is present, the T-wave end was defined as the nadir between the T wave and U wave. cTp-e intervals were calculated by using the Bazett formula. Arithmetic averages of measurements were used for analysis.

SDNN (standard deviation of average of all NN intervals in ECG), minimum NN interval (shortest NN interval in the basal ECG), maximum NN interval (longest NN interval in the basal ECG), mean NN interval (average of all NN intervals in ECG), sNN50 (number of NN intervals' difference greater than 50 ms), pNN50 (the ratio of the number of NN intervals' difference greater than 50 ms to all NN intervals in ECG), and RMSSD (standard deviation of root mean square of all NN intervals in ECG) parameters were calculated on RR intervals findings.

2.5 | Transthoracic echocardiogram (TTE)

All subjects underwent two-dimensional echocardiography examination. We obtained standard parasternal long-axis, midventricular short-axis, long apical axis, apical 2-chamber, and 4-chamber images with the Philips HD11XE, 2012, the Netherlands. Continuous-wave (CW) Doppler of the tricuspid valve regurgitation (TR) tracing was used to measure the pressure difference between the right ventricle and right atrium. In the Bernoulli formula ($P = 4X [TR_{max}]^2$), the value obtained by the CW replacing over TR and the pressure difference between the right ventricle and the right atrium was calculated. The value obtained from the Bernoulli formula is traditionally calculated by the addition of right atrial pressure (RAP) to calculate sPAP. However, the latest ESC (European Society of Cardiology) guidelines recommend the use of the TRmax without additional RAP (Galiè et al., 2016). We used the Vmax value obtained from TR by simply inserting into the formula of Bernoulli.

2.6 | Statistical analysis

Continuous variables were expressed as a mean $\pm$ standard deviation. Categorical variables were expressed as percentages. Student's *t* test and the chi-square test were used for the comparison of continuous and categorical variables. The Pearson correlation test was used to examine the correlation between variables. $p < .05$ was considered to be significant. Statistical analysis was performed using a commercially available statistical package SPSS version 20.0 (IBM Co.).

3 | RESULTS

The sample of our study involved 74 subjects with newly diagnosed COPD and 78 healthy control subjects. The study and control groups were similar in terms of gender and age. There was no difference between the study group and the control group in terms of

smoking habits and number/day rates (25.3 ± 2.7 numbers/day and 24.7 ± 3.1 numbers/day [$t = 1.58, p = .058$], 22.3 ± 6.4 packages/year and 21.7 ± 5.2 packages/year [$t = 1.11, p = .13$]).

There was no difference in age, mean resting HR, arterial blood pressure, QTL-QTcL intervals, Tp-eL and cTp-eL intervals, and BMI between the study and the control groups. There was a statistically significant difference between the study group and the control group in terms of sPAP, RFT, and POS values. Also, there was a statistically significant difference between the study group and the control group in terms of Tp-eR interval, cTp-eR interval, QTR and QTcR intervals, Tp-eR/QTR ratio, and Tp-eR/QTcR ratio. Furthermore, there was no difference between study and control group in terms of Tp-eL, cTp-eL, QTL, and QTcL intervals (Table 1). Also, there were statistically significant differences between QTR-QTL intervals and QTcR-QTcL intervals in the study group, increasingly. While there were no differences between the study and control group in terms of the number of NN intervals and mean NN intervals, SDNN, NN50, pNN50, and RMSSD values measured on the superficial ECG were significantly lower in the study group than in the control group. Besides, there were statistically significant differences between the study and control groups in terms of minimum NN interval and maximum NN interval values (Table 1).

In the study group, there were statistically significant differences between Tp-eR and Tp-eL intervals and cTp-eR and cTp-eL intervals (respectively, $t = 16.12, p < .01$ and $t = 13.06, p < .01$). In addition, in the control group, there were statistically significant differences between Tp-eR, Tp-eL, cTp-eR, and cTp-eL intervals (respectively, $t = -22.89, p < .01$ and $t = -16.55, p < .01$) (Table 1).

While there was a moderate positive correlation between sPAP and Tp-eR interval, Tp-eR/QTR, and moderate positive correlation between sPAP and Tp-eR/QTcR ratios in the study group, a moderate positive correlation was found between sPAP and QTR interval. While there was a moderate positive correlation between sPAP and cTp-eR interval, there was no correlation between sPAP-HR, and there was a statistically significant and weak negative correlation between sPAP and peripheral O_2 saturation values and a weak positive correlation between sPAP and QTcR interval (Figures 1 and 2, Table 2).

Considering the RFT, a strong negative correlation was found between sPAP. This means that the lower values of the FEV_1/FVC are associated with the higher values of the sPAP. There was a moderate negative correlation between FEV_1/FVC and QTR interval, whereas a weak negative correlation was found between QTcR and RFT. There were moderate negative correlations between FEV_1/FVC and Tp-eR interval, Tp-eR/QTR ratio, and Tp-eR/QTcR ratio. In addition, there was a weak positive correlation, statistically significant, between RFT and O_2 saturation value (Figure 3, Table 3).

In the study group, while there were statistically significant moderate negative correlations between Tp-eR and SDNN, RMSSD, and sNN50 values, there was a statistically significant weak negative correlation between Tp-eR and pNN50 value. In addition, in the study group, while there were statistically significant

FIGURE 1 The linear regression graphic of sPAP and the values of Tp-eR interval of the study group. sPAP, systolic pulmonary arterial pressure. $R = .7469$ and $p < .00001$

FIGURE 2 The linear regression graphic of sPAP and RFT of the study group. sPAP, systolic pulmonary arterial pressure. RFT, respiratory function test. $r = -.8546$, $p < .00001$

weak negative correlations between Tp-eL and SDNN and RMSSD values, there were no correlations between sNN50 and pNN50 values (Table 4).

In the control group, there was no correlation between sPAP and both Tp-eR and cTp-eR intervals. Besides, there was a moderate negative correlation between sPAP and RFT. And there was a statistically significant, weak negative correlation between sPAP and POS values. Furthermore, there was no correlation between sPAP and QTR, QTcR, HR, Tp-eL, and cTp-eL (Table 5).

4 | DISCUSSION

Even if the subjects are newly diagnosed with COPD, the Tp-eR interval, indicating the dispersion of transmural repolarization of the right ventricle in COPD subjects, the Tp-eR/QTR, and Tp-eR/QTcR ratio are statistically increased compared to the control group. In addition, there was a strong positive correlation between Tp-eR

interval and sPAP and a moderate negative correlation between Tp-eR interval and FEV_1/FVC .

COPD is independently associated with an increased burden of cardiovascular disease. As well as coronary arterial disease (CAD) and congestive heart failure (CHF), specific ECG abnormalities and cardiac arrhythmias may appear to have a significant impact on the cardiovascular prognosis of COPD subjects. Heart rhythm disorders include not only atrial and ventricular extrasystole, and atrial fibrillation, but also ventricular tachycardia and fibrillation (Goudis, Konstantinidis, Ntalas, & Korantzopoulos, 2015). Subjects with COPD have a 2–3 times increase in the risk of sudden cardiac death compared to the healthy population (Karoli & Rebrov, 2017; Liu, Narayanan, Zhang, Li, & Liu, 2016; Van den Berg et al., 2016). This occurs especially after acute exacerbations of COPD (Lai, DeNardo, Niranjana, & Sriram, 2017; Van Oekelen et al., 2018). Both mechanical events and disorders explain this increase in risk in autonomic functions. Elevations in pulmonary arterial pressure, with or without COPD, were closely associated with sudden cardiac death. The risk of sudden cardiac death was higher in pulmonary hypertension subjects with pulmonary arterial dilatation, some of which are arterial or thromboembolic (Żytkowska et al., 2012).

Many mechanisms have been proposed to determine the relationship between elevation in pulmonary arterial pressure and sudden cardiac death. The mains of these mechanisms are left main compression syndrome, pulmonary arterial dissection, pulmonary arterial rupture, and severe hemoptysis (Demerouti, Manginas, Athanassopoulos, & Karatasakis, 2013). COPD may have systemic effects not only due to increased pulmonary arterial pressure but also by the release of inflammatory mediators (Decramer et al., 2008). Chronic secreted low-intensity inflammatory mediators may cause oxidative stress and endothelial dysfunction, which can lead to heart disease and are the most common causes of morbidity and mortality in COPD. Those who argue that this cannot be explained only because of mechanical reasons have focused on oxidative stress, low-intensity inflammatory mediators, endothelial, and autonomic dysfunction (Eickhoff et al., 2008).

Cardiac autonomic modulation disorders have been found in subjects with COPD, especially in subjects with hypoxemia (Van Gestel & Steier, 2010). To show autonomic neuropathy in subjects with COPD, the heart rate recovery has been investigated. Besides, inadequate baroreceptor response and increased muscle sympathetic activity were demonstrated in subjects with COPD (Mohammed, Meeus, Derom, Da Silva, & Calders, 2015). The autonomic neuropathy in COPD is characterized by a higher heart rate at rest, a decrease in baroreflex sensitivity, a reduction in heart rate variability, and heart rate recovery disorder (Van Gestel & Steier, 2010). These dysfunctions can appear as arrhythmias. Although asystole is more common than ventricular tachycardia and fibrillation in SCD related to COPD, ventricular tachycardia, and fibrillation are also higher than the healthy population (Van den Berg et al., 2016).

The heterogeneity of the duration of the action potential in the heart may cause fatal ventricular arrhythmias. This can be demonstrated by

Variable 1	Variable 2	R-value	Correlation	p-Value
sPAP	RFT	-.85	Strong Negative	<.01
sPAP	POS	-.22	Weak Negative	.049
sPAP	Tp-eR	.74	Moderate Positive	<.01
sPAP	QTR	.55	Moderate Positive	<.01
sPAP	HR	.05	No Correlation	.65
sPAP	QTcR	.28	Weak Positive	.02
sPAP	cTp-eR	.65	Moderate Positive	<.01
sPAP	Tp-eR/QTR ratio	.71	Moderate Positive	<.01
sPAP	Tp-eR/QTcR ratio	.63	Moderate Positive	<.01
sPAP	Tp-eL	.08	No Correlation	.45
sPAP	cTp-eL	.009	No Correlation	.93
sPAP	QTL	.006	No Correlation	.94
sPAP	QTcL	.005	No Correlation	.95

TABLE 2 Correlation table of other values with sPAP of the study group

Abbreviations: cTp-eL, corrected Tp-e interval in the left precordial leads; cTp-eR, corrected Tp-e interval in the right precordial leads; HR, heart rate; POS, peripheral oxygen saturation; QTcL, corrected QT interval in the left precordial leads; QTcR, corrected QT interval in the right precordial leads; QTL, QT interval in the left precordial leads; QTR, QT interval in the right precordial leads; RFT, respiratory function test; sPAP, systolic pulmonary arterial pressure; Tp-eL, Tp-e interval in the left precordial leads; Tp-eR, Tp-e interval in the right precordial leads.

Bold values indicate P -value < .05

FIGURE 3 The linear regression graphic of Tp-eR interval and RFT of the study group. RFT, respiratory function test; Tp-e, T peak-end interval $R = -.6208$, $p < .00001$

the potential mapping of the monophasic effect in the electrophysiology laboratory (Statters, Malik, Ward, & Camm, 1994). Many predictors have been investigated so far to display the electrical heterogeneity in the heart. The most frequently studied one was QT dispersion (QTd). Primarily, QTd was found to be increased in acute exacerbations of COPD, and detection of QTd more than 48 msec was found to be closely related to sudden cardiac death (Lai et al., 2017). Besides, there was no significant difference in QT and QTc interval values with resting and exertion in COPD subjects compared to the control group, and this was not associated with sudden cardiac death (Boutou et al., 2017). In our study, we found no difference between the study and control groups in terms of resting QTL and QTcL values. However, there was a statistically significant difference between the study and control group in terms of QTR and QTcR intervals.

The transmural dispersion disorders of ventricular repolarization have been shown to be associated with ventricular arrhythmias (Watanabe et al., 2004). Increased sympathetic activity and different cardiac autonomic functions are closely related to the heterogeneity of ventricular repolarization and the risk of ventricular arrhythmia (Valensi et al., 2002).

Recently, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio have been accepted as predictors of the disorder of ventricular repolarization dispersion (Gupta et al., 2008; Kors et al., 2008). Increases in Tp-e interval in animal model studies were documented to be closely related to sudden cardiac death (Sicouri & Antzelevitch, 1991). Besides, it is well known that COPD and the increase in Tp-e interval are closely associated with sudden cardiac death (Panikkath et al., 2011; Syromyatnikova et al., 2016; Van den Berg et al., 2016). The rise in Tp-e interval and Tp-e/QT and Tp-e/QTc ratios in subjects with COPD may elucidate the pathophysiological mechanisms of ventricular arrhythmia as showing an increase in heterogeneity of ventricular repolarization. This will help to explain the mechanisms of sudden cardiac deaths in COPD subjects since SCD in COPD subjects increases 2–3 times more than in the average population. However, so far, the Tp-e interval and Tp-e/QT and Tp-e/QTc ratios, which are considered to show the heterogeneity of transmural myocardial repolarization, have not been investigated in subjects with newly diagnosed COPD.

Tp-e interval was investigated in many diseases. Some of those were HIV (Ünal et al., 2018), liver cirrhosis (Akboga et al., 2017), celiac disease (Demirtaş et al., 2017), during migraine attacks (Öztürk et al., 2019), vasospastic angina (Wang et al., 2019), arrhythmogenic right ventricular cardiomyopathy (Cekirdekci & Bagan, 2018), in smokers (İlgenli, Tokatlı, Akpınar, & Kılıçaslan,

TABLE 3 Correlation table of RFT and other values of the study group

Variable 1	Variable 2	R-value	Correlation	p-Value
RFT	HR	-.01	No Correlation	.93
RFT	POS	.29	Weak Positive	.01
RFT	Tp-eR	-.62	Moderate Negative	<.01
RFT	cTp-eR	-.52	Moderate Negative	<.01
RFT	QTR	-.56	Moderate Negative	<.01
RFT	QTcR	.24	Weak Negative	.03
RFT	Tp-eR/QTR	-.70	Moderate Negative	<.01
RFT	Tp-eR/QTcR	-.63	Moderate Negative	<.01

Abbreviations: cTp-eL, corrected Tp-e interval in the left precordial leads; cTp-eR, corrected Tp-e interval in the right precordial leads; HR, heart rate; POS, peripheral oxygen saturation; QTcL, corrected QT interval in the left precordial leads; QTcR, corrected QT interval in the right precordial leads; QTL, QT interval in the left precordial leads; QTR, QT interval in the right precordial leads; RFT, respiratory function test; sPAP, systolic pulmonary arterial pressure; Tp-eL, Tp-e interval in the left precordial leads; Tp-eR, Tp-e interval in the right precordial leads.

Bold values indicate *P*-value < .05

TABLE 4 Correlation table of Tp-eR and Tp-eL values with HRV values of the study group

Variable 1	Variable 2	R-value	Correlation	P-value
Tp-eR	SDNN	-.63	Moderate Negative	<.01
Tp-eR	RMSSD	-.56	Moderate Negative	<.01
Tp-eR	sNN50	-.51	Moderate Negative	<.01
Tp-eR	pNN50	-.45	Weak Negative	<.01
Tp-eL	SDNN	-.35	Weak Negative	<.01
Tp-eL	RMSSD	-.27	Weak Negative	.019
Tp-eL	sNN50	-.21	No Correlation	.072
Tp-eL	pNN50	-.20	No Correlation	.087

Abbreviations: pNN50, the ratio of the number of NN intervals' difference greater than 50 ms to all NN intervals in ECG; RMSSD, standard deviation of root mean square of all NN intervals in ECG; SDNN, standard deviation of average of all NN intervals in ECG; sNN50, number of NN intervals' difference greater than 50 ms; Tp-eL, Tp-e interval in the left precordial leads; Tp-eR, Tp-e interval in the right precordial leads.

Bold values indicate *P*-value < .05

TABLE 5 Correlation table of other values with sPAP of the control group

Variable 1	Variable 2	R-value	Correlation	p-Value
sPAP	Tp-eR	.11	No Correlation	.17
sPAP	cTp-eR	.09	No Correlation	.19
sPAP	QTR	-.10	No Correlation	.38
sPAP	QTcR	-.01	No Correlation	.91
sPAP	RFT	-.67	Moderate Negative	<.01
sPAP	HR	.005	No Correlation	.96
sPAP	Tp-eL	.18	No Correlation	.09
sPAP	cTp-eL	.18	No Correlation	.09
sPAP	POS	-.22	Weak Negative	.044

Abbreviations: cTp-eL, corrected Tp-e interval in the left precordial leads; cTp-eR, corrected Tp-e interval in the right precordial leads; HR, heart rate; POS, peripheral oxygen saturation; QTcL, corrected QT interval in the left precordial leads; QTcR, corrected QT interval in the right precordial leads; QTL, QT interval in the left precordial leads; QTR, QT interval in the right precordial leads; RFT, respiratory function test; sPAP, systolic pulmonary arterial pressure; Tp-eL, Tp-e interval in the left precordial leads; Tp-eR, Tp-e interval in the right precordial leads.

Bold values indicate *P*-value < .05

2015), and in many other diseases. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were found to be increased, and it was concluded that these could be related to increased SCD. Also, in a study with a small number of cases, hypertensive subjects with left ventricular hypertrophy were compared with subjects with pulmonary hypertension, and the control group consisted of healthy subjects. Subjects with systemic hypertension with left ventricular hypertrophy had prolonged Tp-e interval in the left precordial leads compared to the right. Furthermore, subjects with pulmonary arterial hypertension were found to have a similar Tp-e interval in the right and left precordial leads. Also, subjects with pulmonary arterial hypertension were found to have longer Tp-e interval in the right precordial leads than in the right precordial leads of hypertensive subjects with left ventricular hypertrophy and control group (Hlaing et al., 2005).

Lower POS is an expected finding in subjects with COPD. As COPD severity increases, POS decreases in subjects with COPD (Vogelmeier et al., 2017). In subjects with COPD, the decrease in oxygen saturation can cause pulmonary hypertension, systemic inflammation, a decrease in quality of life, and an increase in mortality in the long term (Kent, Mitchell, & McNicholas, 2011). Long-term administration of oxygen leads to a reduction in the risk of acute exacerbation and mortality in subjects with COPD (Stoller, Panos, Krachman, & Doherty, 2010). In our study, peripheral oxygen saturation was found to be lower statistically significant than the control group.

In our study, considering QTR-QTcR and QTL-QTcL intervals, there was no difference between study and control groups in terms of QTL-QTcL, and there was a statistically significant difference between study and control group in terms of QTR and QTcR intervals. Furthermore, we found a statistically significant increase in Tp-eR interval, Tp-eR/QTR ratio, and Tp-eR/QTcR ratio in the study group compared to the control group. And there was no difference between the study and control group considering Tp-eL and cTp-eL. We thought that this might be due to the balance disorders in neurohumoral equilibrium in COPD subjects. In this present study, we found the increased Tp-eR, Tp-eR/QTR ratio, and Tp-eR/QTcR ratio as reflections of increased risk of ventricular arrhythmias due to altered ventricular repolarization.

5 | STUDY LIMITATIONS

In our study, the number of cases was small, and data in healthy subjects can be obtained with more extensive case studies. Also, we calculated RR, QT, and Tp-e interval values and the parameters of heart rate variability on only superficial ECG manually via digital caliper and magnifying glass. Besides, we did not make the monitoring of 24-hr Holter to observe ventricular arrhythmias and to evaluate the parameters of 24-hr heart rate variability. In addition, we did not corroborate our findings using another marker, including T-wave alternans and T-wave area dispersion. Furthermore, since the Tp-e interval cannot wholly demonstrate the heterogeneity of the whole

repolarization of the ventricle, care should be taken when interpreting the Tp-e interval in the superficial ECG alone. Therefore, Tp-e interval findings should corroborate with another newly markers, T-wave alternans, and T-wave area dispersion.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. There is no source(s) of support in the form of grants, equipment, and drugs. All expenses are paid by the authors. The authors state that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

AUTHOR CONTRIBUTIONS

A.C. and H.O. made literature search, data collection, manuscript preparation, and review of the manuscript. A.C. also made study design and analysis of data. M.H.T. made manuscript preparation and review of the manuscript. The study was made in Department of Cardiology, Sincan State Hospital. The research data were not previously presented. All expenses for the study were made by the authors, and there are no sponsors.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Turkey Research Committee and with the 1964 Helsinki Declaration and its later comparable ethical standards. There is no Ethics Committee in our hospital. The present study permit was obtained from hospital management. Informed written consent was obtained from each of the patients participating in the study.

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