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Evaluation of repolarization dispersion in patients with idiopathic pulmonary fibrosis

Ferhat Eyyupkoca[1], Siho Hidayet[2], Mehmet Sait Altintas[3], Yasin Yuksel[4], Baris Demirkol[5], Erdogan Cetinkaya[5]

[1]Dr. Nafiz Korez Sincan State Hospital, Department of Cardiology, Ankara, Turkey
[2]Inonu University, Faculty of Medicine, Department of Cardiology, Malatya, Turkey
[3]Istanbul Yedikule Training and Research Hospital, Department of Cardiology, Istanbul, Turkey
[4]Istanbul Training and Research Hospital, Department of Cardiology, Istanbul, Turkey
[5]Istanbul Yedikule Training and Research Hospital, Department of Pulmonology, Istanbul, Turkey

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a serious lung disease of unknown etiology and characterized by interstitial fibrosis. The patients usually present with potentially fatal cardiac arrhythmias. This study aimed to investigate indicators of arrhythmia based on electrocardiography (ECG) in patients with IPF. ECG indicators of ventricular depolarization (VD) and repolarization (VR) (QT, QT_c, QT_d, QT_{dc}, Tp-e, JT and JT_c intervals, Tp-e / QT ratio, Tp-e / QT_c ratio, Tp-e / JT ratio, and Tp-e / JT_c ratio) were analyzed retrospectively in patients with IPF (n:52) and compared with the healthy control group (n:52). The mean QRS interval was lower in patients with IPF compared to the control group, indicators of VD and VR were higher in patients with IPF compared to the control group ($p < 0.05$). A positive correlation was found between indicators of VD and VR and inflammation markers (CRP and cTn-I) ($p < 0.05$). We found that indicators of VD and VR were higher in patients with IPF and that is positively correlated with inflammatory markers. Inflammation in cases of IPF may be associated with the development of malignant or chronic cardiac arrhythmias.

Keywords: Arrhythmias, electrocardiography, idiopathic pulmonary fibrosis, repolarization

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown cause, which is seen mostly in older adults, and is characterized by thickening of the walls of the air sacs (alveoli) in the lungs and related with the radiologic and histopathologic pattern of usual interstitial pneumonia [1,2]. Atrial arrhythmias are common in patients with IPF. Life-threatening arrhythmias may develop in IPF due to hypoxia, pulmonary hypertension, chronic inflammation, neural, pericardial, and atrial infections, or changes in the anatomical position of the heart in the mediastinum during or after surgery [3-5].

Ventricular repolarization (VR) can be assessed non-invasively with electrocardiography (ECG) parameters (such as Tp-e interval, QT dispersion, Tp-e / QT ratio, and Tp-e / QT_c ratio). The literature on the ECG characteristics of IPF patients is mostly based on cardiopulmonary exercise testing and surface ECG parameters, such as the QT, PR, and QRS intervals [6,7]. To the best of our knowledge, there are limited studies of VR in IPF cases. This study aimed to investigate indicators of arrhythmia based on ECG in patients with IPF.

Materials and Methods

Study population

The study, which was planned as a retrospective cross-sectional design from February 2019 to August 2019, included 52 healthy individuals (n=52) and patients with clinically stable IPF (n=52). Individuals of both groups ranged in age from 18 to 80 years old. IPF was diagnosed according to the 2018 international diagnostic criteria [8]. While selecting the healthy control group, we evaluated the patients presenting with the general examination (ICD code: Z00.8) between February 2019 and August 2019. We identified 180 patients without any health problems in the 6 months. Afterward, a 1:1 matching method was performed between the control group and IPF patients in terms of age and gender. All aspects of the research were carefully designed to comply with the Declaration of Helsinki, update 2013, as well as the principles of good clinical

***Corresponding Author:** Ferhat Eyyupkoca, Dr. Nafiz Korez Sincan State Hospital, Department of Cardiology, Ankara, Turkey
E-mail: eyupkocaferhat@gmail.com

practices. The study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Istanbul Training and Research Hospital (Decision Date/No: 24.07.2020 / 2482). The consent of all participants was obtained in both verbal and written form before the study began.

The exclusion criteria of the study were history of a lung transplant, hypertension, diabetes mellitus, cardiac failure, congenital heart diseases, history of asthma, history of coronary artery disease, history of pulmonary embolism, chronic obstructive lung disease, and any anti-arrhythmic drug usage.

The clinical data (laboratory, echocardiographic, and ECG parameters) and the demographic data (age, gender, body weight, and height) were obtained from patient files of the hospital's electronic information system.

Electrocardiography

The 12 lead ECG recorder set at 50 mm/s paper speed and 10 mm/mV was used (Nihon Kohden, Tokyo/Japan). All ECGs were evaluated by a single cardiologist who was blinded by patients. The ECG indicators [such as minimum and maximum P wave duration (P_{min}, P_{max}), P wave dispersion (P_d), PR distance (PR_d), minimum and maximum QT wave duration (QT_{min}, QT_{max}), QT dispersion (QT_d), heart rate-corrected QT interval (QT_c), QRS duration (QRS_d), JT interval (JT_c) and Tpeak to Tend (Tp-e)] were measured in all derivations and their means were calculated. The onset and offset of the P wave were evaluated as the junction between the P wave pattern and the isoelectric line. The P_{max} was accepted as the lengthiest P wave and the lengthiest atrial conduction time. The P_d was computed with the formula $P_d = P_{max} - P_{min}$ [9]. The QT interval was evaluated as the distance between the onset of the Q wave and the offset of the T wave. The QT_c was computed using Bazett's formula [10]. The JT interval was evaluated as the distance between the onset J wave and the end T wave. The JT_c measurement was computed with the formula $JT_c = QT_c - QRS_d$ [11].

Echocardiography

Echocardiography was evaluated using a 2.5-MHz transducer and the Vivid-5 System (GE Medical Systems, Horten/Norway) by an experienced cardiologist following guidelines of the American Society of Echocardiography (ASE). Left ventricular ejection fraction (LV EF) was computed using the modified Simpson's biplane method. The early and late diastolic peak transmitral flow velocity (E and A) was measured by PW Doppler and the E / A ratio was computed.

Laboratory testing

Results of the tests of blood samples were obtained from patient files as described above. The fasting blood glucose, lipid panel, liver function tests (ALT and AST), kidney function test (creatinine and blood urea nitrogen) as determined by colorimetric method (Cobas 8000, Roche, Germany) were all noted, and complete blood count parameters (BS-200, Mindray, Shenzhen, China), C – reactive protein (CRP) (turbidimetric method, Beckman Coulter 5800), and ESR (Diesse Vesmatic Cube 200) were also recorded. Levels of cardiac troponin I (cTn-I) were obtained by measurements from lithium-heparinized plasma using the AQT90 FLEX cTn-I immunoassay (Radiometer Medical ApS, Denmark).

Statistical analysis

The normality distribution of numerical variables was tested with the Kolmogorov- Smirnov test, and those with normal distribution were shown with mean ± standard deviation (SD) and those without normal distribution with median (min-max). Categorical variables were shown numbers and percentages. Chi-square and Fisher's Exact Chi-square test were used to compare categorical variables. The student's T-test was utilized to compare numerical variables between the IPF group and the control group showing normal distribution, while the Mann-Whitney U test was utilized to compare those numerical variables not showing normal distribution. The relationship between numerical variables was analyzed by Pearson and Spearman correlation analysis. All statistical analyzes were evaluated with STATA software (Stata Corp LLC, TX, USA) and the p-value < 0.05 was considered significant.

Results

The mean age of patients with IPF was 65.7±9.5 years, and the mean age of the healthy controls was 64.8±8.6 years. The mean white blood cell count (10.4±2.7 vs 7.3±1.8 $x10^3/\mu L$, $p < 0.001$), median erythrocyte sedimentation rate (30 vs 8 mm/hr, $p < 0.001$), median CRP (5.8 vs 1 mg/L, $p < 0.001$), mean low density lipoprotein cholesterol (134.3±34.9 vs 86.3±27.3 mg/dL, $p < 0.001$), median cTn-I (5 vs 0 ng/mL, $p < 0.001$) were higher in patients with IPF compared to the control group. Distributions of demographic and laboratory findings are shown in Table 1.

The mean left atrium (LA) diameter (37.7±3.3 vs 31.0±2.5 mm, $p < 0.001$), left ventricular end diastolic diameter (46.8±4.1 vs 35.4±3.2 mm, $p < 0.001$), presence of tricuspid regurgitation (15.4% vs 0%, $p = 0.010$), and mean PABs (37.3±13.4 vs 18.0±2.3 mm Hg, $p < 0.001$) were higher in patients with IPF compared to the control group, and the mean LV EF (58.8±2.6 vs 61.0±4.6 %; $p = 0.007$) was lower (Table 2).

The mean QT_c (424.0±22.2 vs 401.0±31.7 msn, $p < 0.001$), mean Tp-e (96.9±13.1 vs 75.4±10.3 msn, $p < 0.001$), mean JT_c (328.8±17.4 vs 309.1±32.8 msn, $p < 0.001$), mean Tp-e / QT ratio (25.6±3.5 vs 20.8±3.0%, $p < 0.001$), mean Tp-e / QT_c ratio (22.9±3.5 vs 18.9±2.6%, $p < 0.001$), mean Tp-e / JT ratio (33.0±4.1 vs 27.1±4.3%, $p < 0.001$), and mean Tp-e / JT_c ratio (29.6±4.2 vs 24.6±3.8%, $p < 0.001$) were higher in patients with IPF compared to the control group, and the mean QRS duration (85.8±11.4 vs 90.9±11.4 msn, $p = 0.02$) was lower (Table 2).

There was a negative correlation between the QRS duration and QT_d ($r = -0.31$, $p = 0.01$), QT_c ($r = -0.32$, $p = 0.01$), QT_{mean} ($r = -0.32$, $p = 0.01$), JT ($r = -0.31$, $p = 0.02$) ve JT_c ($r = -0.39$; $p < 0.001$) levels in the whole population.

There were a positively correlation between the CRP and Tp-e / QT ($r = 0.35$, $p < 0.001$), Tp-e / QT_c ($r = 0.36$, $p < 0.001$), Tp-e / JT ($r = 0.37$, $p < 0.001$), and Tp-e / JT_c ($r = 0.38$, $p < 0.001$) ratios (Table 3).

Table 1. Demographic and laboratory findings

Variables	Control n=52	IPF n=52	p
Demographic findings			
Gender, n (%)			
Female	12(23.1)	10(19.2)	0.81
Male	40(76.9)	42(80.8)	
Age, years	64.8±8.6	65.7±9.5	0.61
BMI, kg/m²	26.4±4.7	25.9±5.2	0.60
Laboratory findings			
Hemoglobin, g/dL	14.6±1.6	14.1±1.7	0.08
WBC, x10³/µL	7.3±1.8	10.4±2.7	<0.001
Platelet, x10³/µL	260.2±56.9	252.6±60.9	0.51
ESR, mm/hr	8(2-17)	30(4-87)	<0.001
Glucose, mg/dL	88.1±6.4	92.4±25.8	0.24
Urea, mg/dL	25.6±6.3	27.6±8.4	0.17
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.34
Sodium, mmol/L	138.8±2	137.5±6.1	0.32
Potassium, mmol/L	4.3±0.3	4.4±0.5	0.12
AST, U/L	17(11-42)	18.5(6-38)	0.20
ALT, U/L	16(5-89)	15(6-30)	0.66
CRP, mg/dL	1(0.3-9)	5.8(0.4-203.5)	<0.001
Procalcitonin, %	0(0-0.1)	0.3(0-2.4)	<0.001
LDL, mg/dL	86.3±27.3	134.3±34.9	<0.001
HDL, mg/dL	49.3±10.7	51.0±14.8	0.51
Triglyceride, mg/dL	96.5(37-518)	125(59-419)	0.01
cTn-I, ng/mL	0(0-0.1)	5(1.8-186.8)	<0.001
CK, U/L	25(15-110)	58(23-174)	<0.001
CK-MB, U/L	10(5-15)	14(7.7-27.5)	<0.001

Numerical variables were shown as mean ± standard deviation or median (min-max).
Categorical variables were shown as numbers (%). Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK: creatine kinase, CK-MB: creatine kinase myocardial band, CRP: C – reactive protein, cTn-I: cardiac troponin I, ESR: erythrocyte sedimentation rate, HDL: high-density lipoprotein, LDH: lactate dehydrogenase, LDL: low-density lipoprotein, PCT: procalcitonin, WBC: white blood cell.

Table 2. Echocardiographic and ECG findings

Variables	Control n=52	IPF n=52	p
Echocardiographic findings			
EF, %	61.0±4.6	58.8±2.6	0.007
E/A ratio	0.9±0.2	0.7±0.1	<0.001
LA diameter, mm	31.0±2.5	37.7±3.7	<0.001
LVEDD, mm	35.4±3.2	46.8±4.1	<0.001
MR, n (%)	0	2(3.8)	0.48
TR, n (%)	0	8(15.4)	0.01
TAPSE, mm	22.3±3.8	20.5±4.2	0.02
sPAB, mm Hg	18.0±2.3	37.3±13.4	<0.001
ECG findings			
HR, beats / minute	74.4±17.1	76.8±16.1	0.47
P_{max}, msn	101.4±10.5	112.8±10.8	<0.001
P_{min}, msn	80.7±10.7	85.1±8.6	0.02
P_d, msn	19.4(4-54)	26(12-50.4)	<0.001
PR_d, msn	150.4±17.1	163.5±27.6	0.005
QT_{max}, msn	377.4±30.0	391.1±31.1	0.02
QT_{min}, msn	352.0±29.0	367.4±30.5	0.009
QT_d, msn	20.4(5.6-42.4)	28(10-55.6)	0.03
QT_c, msn	401.0±31.7	424.0±22.2	<0.001
QT_{mean}, msn	364.6±28.9	379.3±30.6	0.01
QT_{dc} ,msn	21.6(5.2-47.4)	25.2(13.7-54.1)	0.02
QRS_d, msn	90.9±11.4	85.8±11.4	0.02
JT, msn	281.0±29.1	294.0±22.5	0.01
JT_c, msn	309.1±32.8	328.8±17.4	<0.001
Tp-e, msn	75.4±10.3	96.9±13.1	<0.001
Tp-e / QT, (%)	20.8±3.0	25.6±3.5	<0.001
Tp-e / QT_c, (%)	18.9±2.6	22.9±3.5	<0.001
Tp-e / JT, (%)	27.1±4.3	33.0±4.1	<0.001
Tp-e / JT_c, (%)	24.6±3.8	29.6±4.2	<0.001
RR	0.8±0.2	0.8±0.2	0.33

Numerical variables were shown as mean ± standard deviation or median (min-max).
Categorical variables were shown as numbers (%). Abbreviations: EF: ejection fraction, LA: left atrium, MR: mitral regurgitation, TR: tricuspid regurgitation, PAP: pulmonary artery pressure, HR: heart rate, Pmax: maximum P wave duration, Pmin: minimum P wave duration, Pd: P wave dispersion, PRd: PR distance, QTmax: maximum QT wave duration, QTmin: minimum QT wave duration, QTd: QT dispersion, QTc: corrected QT interval, QRSd: QRS interval, JTc: JT interval, Tp-e: Tpeak to Tend

Table 3. ECG parameters associated with inflammation markers and LA diameter

Variables	hs-CRP		cTn-I		LA diameter	
	r	p	r	p	r	p
CRP	-	-	0.56	<0.001	0.44	<0.001
cTn-I	0.56	<0.001	-	-	0.67	<0.001
LA diameter	0.44	<0.001	0.67	<0.001	-	-
HR	0.15	0.15	0.14	0.15	0.001	0.98
P_{max}	0.19	0.07	0.38	<0.001	0.39	<0.001
P_{min}	-0.03	0.75	0.16	0.10	0.34	0.009
P_d	0.34	0.02	0.35	0.01	0.33	0.03
PR_d	0.08	0.42	0.29	0.03	0.31	0.03
QT_{max}	-0.07	0.51	-0.13	0.18	-0.07	0.46
QT_{min}	-0.03	0.73	0.33	0.02	0.36	0.006
QT_d	-0.02	0.84	0.32	0.02	0.37	0.002
QT_c	-0.007	0.94	0.05	0.61	-0.08	0.41
QT_{mean}	0.17	0.10	0.41	<0.001	0.35	<0.001
QT_{dc}	-0.04	0.70	0.33	0.02	0.32	0.003
QRS_d	0.007	0.94	0.09	0.36	-0.09	0.33
JT	-0.09	0.38	0.34	0.01	0.32	0.01
JTc	0.05	0.64	0.38	<0.001	0.33	0.006
Tp-e	0.33	0.002	0.62	<0.001	0.42	<0.001
Tp-e / QT	0.35	<0.001	0.51	<0.001	0.30	0.002
Tp-e / QT_c	0.36	<0.001	0.44	<0.001	0.31	0.002
Tp-e / JT	0.37	<0.001	0.46	<0.001	0.33	0.001
Tp-e / JT_c	0.38	<0.001	0.39	<0.001	0.32	0.003
RR	-0.15	0.15	-0.14	0.15	-0.03	0.71

* $p < 0.05$ shows statistical significance.

Abbreviations: CRP: C – reactive protein, cTn-I: cardiac troponin I, EF: ejection fraction, LA: left atrium, MR: mitral regurgitation, TR: tricuspid regurgitation, PAP: pulmonary artery pressure, HR: heart rate, Pmax: maximum P wave duration, Pmin: minimum P wave duration, Pd: P wave dispersion, PRd: PR distance, QTmax: maximum QT wave duration, QTmin: minimum QT wave duration, QTd: QT dispersion, QTc: corrected QT interval, QRSd: QRS interval, JTc: JT interval, Tp-e: Tpeak to Tend

Discussion

In this study, the ECG indicators show that IPF patients are at risk of arrhythmia. We found that the Tp-e interval was prolonged and the TP-e / QT, Tp-e / QT_c, Tp-e / JT, and Tp-e / JT_c ratios were higher in patients with IPF. There was a positive correlation between the indicators of VR and VD and inflammation markers.

Atrial arrhythmias, such as AF and AFL, are common in patients with IPF [3,12]. The mechanism of arrhythmias in IPF is not yet clear. Arrhythmias are often associated with VR abnormalities [13]. Similarly, we found signs of VR and VD abnormalities in patients with IPF. The mechanism may be related to enlargement and delayed activation of the left atrium. Prolonged P wave dispersion indicates inhomogeneous and discontinuous atrial conduction [13]. Left atrial enlargement can cause prolonged depolarization and prolonged P wave dispersion, potentially leading to frequent arrhythmia episodes and chronic arrhythmia [14,15]. These findings explain the positive correlation between P wave parameters and left atrial diameter. This association suggests that the atrial myocardium of patients with IPF presents unique electrophysiological characteristics.

Prolonged QT and JT intervals, which are indicative of VR abnormalities, were determined in patients with IPF. The increased QT dispersion is related to an increase in VR heterogeneity and consequently with ventricular instability, and it is an important indicator of malignant arrhythmias [16]. Despite being a component of QT, the JT interval has been proposed as a better indicator of VR than the QT [17]. However, QRS duration, which represents VD, can influence QT and JT intervals [18]. Our findings suggest that patients with IPF have shorter QRS durations. A decreased QRS interval or a narrow QRS complex may be associated with aberrant conduction of supraventricular complexes [19,20]. Our finding of a negative correlation between QRS duration and QT and JT intervals may support this hypothesis.

The Tp-e interval is the accepted transmural dispersion index of VR [21]. Bodyweight and heart rate can cause a difference in the Tp-e interval, but the Tp-e / QT ratio is not affected by variations in heart rate. It is suggested that the Tp-e / QT ratio is a better index of VR compared to QT parameters [22]. In our study, Tp-e / QT_c and TP-e / JT_c ratios, both of which were considered important indices of arrhythmogenesis, were increased in patients with IPF and positively correlated with inflammation. This correlation may be due to increased cytokine levels, such as interleukin-6 and TNF-α, which can serve as triggers for the chronic inflammation arrhythmias that are prominent in IPF prognosis [5]. VR may be affected by the changes in intrathoracic pressures due to airway obstruction and changes in the mechanical environment of the heart due to lung hyperinflation [23,24].

The major limitation of this study is the retrospective cross-sectional design. The retrospective design prevented us from collecting adequate data on hemodynamic changes. Another major limitation is not having used 24-hour Holter ECG recordings, which provide more accurate data on dispersion of VR. A third limitation is not having investigated the correlation between medications used by IPF patients and ECG parameters. The literature reports cardiovascular side effects, such as conduction abnormalities, QT

prolongation, and QT and QRS prolongation, with tyrosine kinase inhibitors such as nintedanib [25, 26].

We conclude that prolonged VR and VD in patients with IPF and that this increase is correlated with inflammatory markers. Combined with inflammation, these abnormalities can have fatal consequences in patients with IPF who are at risk of arrhythmia. Current findings demonstrate the importance of ECG evaluation in routine controls, as the atrial myocardium of patients with IPF reflects unique electrophysiological features. This may be a guide to adverse cardiac events in the management of IPF. Further large-scale prospective studies are needed to clarify the prognostic importance of these parameters in predicting arrhythmias in IPF.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
The Local Ethics Committee approval from University of Health Sciences Istanbul Training and Research Hospital (Decision Date/No: 24.07.2020 / 2482).

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