ORIGINAL ARTICLE

Evaluation of Tp-e interval and Tp-e:QT and Tp-e:QTc ratios in patients infected with HIV and using antiretroviral therapy

Antiretroviral kullanan HIV enfekte hastalarda Tp-e aralığının, Tp-e: QT ve Tp-e: QTc oranlarının değerlendirmesi

Şükrü Çetin M.D.[1], Ayşe Şabablı Çetin M.D.[2], Emine Altuntaş M.D.[1], Ali Bayraktar M.D.[1]

[1]Department of Cardiology, Sancaktepe Şehit Prof Dr İlhan Varank Training and Research Hospital, İstanbul, Turkey
[2]Department of Clinical Microbiology and İnfectious Disease, Sancaktepe Şehit Prof Dr İlhan Varank Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Sudden cardiac death (SCD) is one of the causes of death among patients infected with human immunodeficiency virus (HIV). The T peak to T end interval (Tp-e interval) is a parameter that is used in the prediction of SCD. The aim of this study was to investigate the difference in Tp-e interval and Tp:QT and Tp:corrected QT interval (QTc) ratios between patients infected with HIV and healthy individuals as well as in other factors affecting patients infected with HIV.

Methods: A total of 83 patients infected with HIV with negative HIV ribonucleic acid (RNA) levels who were receiving antiretroviral therapy (ART) and 83 healthy individuals were included in this study. All the participants underwent electrocardiography, their Tp-e and QT intervals were measured, and QTc intervals and Tp-e:QT and Tp-e:QTc ratios were calculated. In addition, in the patients infected with HIV, CD4 and CD8 T-cell count and HIV RNA levels were measured.

Results: The Tp-e interval was found to be longer and the Tp-e:QT and Tp-e:QTc ratios were found to be higher in patients infected with HIV. Nadir CD4 was observed to be an independent predictor of Tp-e interval (p=0.014, β=-0.28). Furthermore, correlation analysis revealed a negative correlation of the nadir CD4 level and CD4:CD8 ratio with Tp-e interval and Tp-e:QT ratio.

Conclusion: Low nadir CD4 and a reversed CD4:CD8 ratio in patients infected with HIV receiving ART were found to be associated with a prolonged Tp-e interval and increased Tp-e:QT and Tp-e:QTc ratios. Thus, more attention should be taken in terms of SCD in patients infected with HIV, especially in those with low nadir CD4 and reversed CD4:CD8 ratio.

ÖZET

Amaç: Ani kardiyak ölüm (AKÖ), insan bağışıklık yetmezliği virüsü (HIV) ile enfekte hastalarda ölüm nedenlerindendir. Tp-e intervali ve Tp-e: QT oranı AKÖ öngörmede kullanılan parametrelerdendir. Bu çalışmanın amacı HIV ile enfekte hastalarda sağlıklı bireylere göre Tp-e aralığı, Tp-e: QT ve Tp-e: QTc oranlarının arasında farklılığın varlığını ve farklılık varsa etki eden faktörleri araştırmaktır.

Yöntemler: Araştırmaya antiretroviral (ART) ilaç kullanıp HIV-ribonükleik asit (RNA) seviyesi negatif olan 83 HIV enfekte hasta ile 83 sağlıklı birey çalışmaya alındı. Tüm katılımcılara elektrokardiyografi (EKG) çekilip, Tp-e ve QT intervali ölçüldü ve QTc intervali, Tp-e: QT ve Tp-e: QTc oranları hesaplandı. Ayrıca HIV enfekte hastalarda CD4 ve CD8 T hücre sayısı ve HIV RNA düzeyi bakıldı.

Bulgular: HIV enfekte hastalarda daha uzun Tp-e interval ve daha yüksek Tp-e: QT ve Tp-e: QTc oranları saptandı. Nadir CD4, Tp-e göstermede bağımsız prediktör olarak izlendi (p: 0.014 β: -0.28).Ayrıca nadir CD4 ve CD4/CD8 oranı ile Tp-e intervali ve Tp-e: QT oranı arasında negatif korelasyon izlendi.

Sonuç: ART kullanan HIV ile enfekte hastalarda düşük nadir CD4 ve ters dönmüş CD4/C8 oranı, Tp-e intervalinde uzama ve Tp-e: QT oranında artış ile ilişkili bulundu. HIV enfekte hastalarda özellikle de düşük nadir CD4 ve CD4/CD8 oranı olanlarda AKÖ açısından dikkatli olunmalıdır.

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Correspondence: Şükrü Çetin, M.D. Department of Cardiology, Sancaktepe Şehit Prof Dr İlhan Varank Training and Research Hospital, 34785, İstanbul, Turkey
Tel: +905077885508 e-mail: chetinsukru@hotmail.com

Ease of access to antiretroviral therapy (ART) has reduced acquired immunodeficiency syndrome (AIDS)-related deaths; however, the non-AIDS–related mortality rate, including cardiovascular events, has increased.[1] The risk of cardiovascular events is approximately 2 times higher for patients infected with human immunodeficiency virus (HIV) receiving ART than for healthy individuals.[2] Cardiovascular diseases (CVDs) are responsible for a significant proportion of sudden cardiac deaths (SCDs), and the risk of SCDin the HIV-infected population cannot be ignored.[3-4] Although the mechanisms of SCD in patients with AIDS are not entirely clear, chronic inflammation and continuous immune activation are thought to be the causes.[5] Low CD4 T-cell levels and an inverted CD4:CD8 ratio may also lead to SCD.[6]

Electrocardiography (ECG), an easily accessible and feasible examination tool, is a convenient method for the evaluation of SCD.[7] The Tpeak to Tend interval (Tp-einterval),that is,the interval between the peak point and the end point of the T-wave, is thought to be associated with the dispersion of ventricular repolarization and the transmural dispersion of repolarization.[8] Ventricular arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), have been associated with SCD.[9] In addition, Tp-e interval, Tp-e:QT ratio,and Tp-e:corrected QT interval (QTc) ratio have been shown to be associated with ventricular arrhythmias.[10,11]

Some studies have measured ventricular repolarization by calculating QT dispersion and QTc intervals in patients infected with HIV.[12] The aim of this study was to evaluate ventricular repolarization in patients infected with HIV by using Tp-e intervals andTp-e:QT and Tp-e:QTc ratios.

METHODS

Study population

A total of 83 outpatients (95% male) and 83 healthy controls (95% male) were included in this prospective study (Fig.1). Patients with diabetes, hypertension, an active infection, thyroid dysfunction, serum electrolyte impairment, uncontrolled HIV, a history of cardiac disease, or a family history of SCD were excluded. The study was approved by Clinical Research Ethic Committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval Date: December 26, 2019; Approval Number: 065). All participants were informed about the research, and they signed informed consent forms.

Abbreviations:

A	*Peak velocity of the late*
AIDS	*Acquired immunodeficiency syndrome*
ART	*Antiretroviral therapy*
CVD	*Cardiovascular disease*
E	*Peak velocity of the early*
E'	*Early diastolic velocity*
ECG	*Electrocardiography*
GLS	*Global longitudinal strain*
HIV	*Human immunodeficiency virus*
LDL	*Low-density lipoprotein*
LVEF	*Left ventricular ejection fraction*
LVM	*Left ventricular mass*
QTc	*Corrected QT interval*
SCD	*Sudden cardiac death*
Tp-e interval	*T peak to Tend interval*
TSH	*Thyroid-stimulating hormone*
VF	*Ventricular fibrillation*
VT	*Ventricular tachycardia*

Electrocardiographic assessment

A total of 12 lead ECGs were performed on all participants and were evaluated by 2 experienced cardiologists who were blinded to the participants' clinical status. An ECG paper speed of 50 mm/s and an amplitude of 10 mm/mV were used for the analyses. Eachparticipant's QRS duration, QT interval, and Tp-e interval were measured manually. Tp-e interval was measured bythe tangent method, which defines the peak maximum T-wave deflection from the isoelectric line and the T-end as the intersection of the isoelectric line and the tangent to the downslope of the T-wave. The Tp-e interval measurements were performed in ECG leads V2 and V5. QTc was calculated using Bazett's formula.[13] The Tp-e:QT and Tp-e:QTc ratios were calculated by dividing the Tp-e interval by the QT interval and QTc. The intra and interobserver variation coefficients were less than 0.5%.

Echocardiographic measurements

Echocardiographic measurements were performed using the Philips EPIQ7 ultrasound system (Medical Healthcare Solutions, Inc.; Andover, MA, USA) equipped with an S5-1 transducer probe. The echocardiographic analyses were performed by 2 cardiologists who were blinded to the study groups. Single-lead echocardiographic recordings were simoultaneously obtained during the echocardiographic recordings. A 2-dimensional, M-mode, and color-flow Doppler echocardiography was performed in accordance with the guidelines.[14]

The biplane Simpson's method was used for left ventricular ejection fraction (LVEF) measurements in the apical 4-chamber view. The left ventricular end-di-

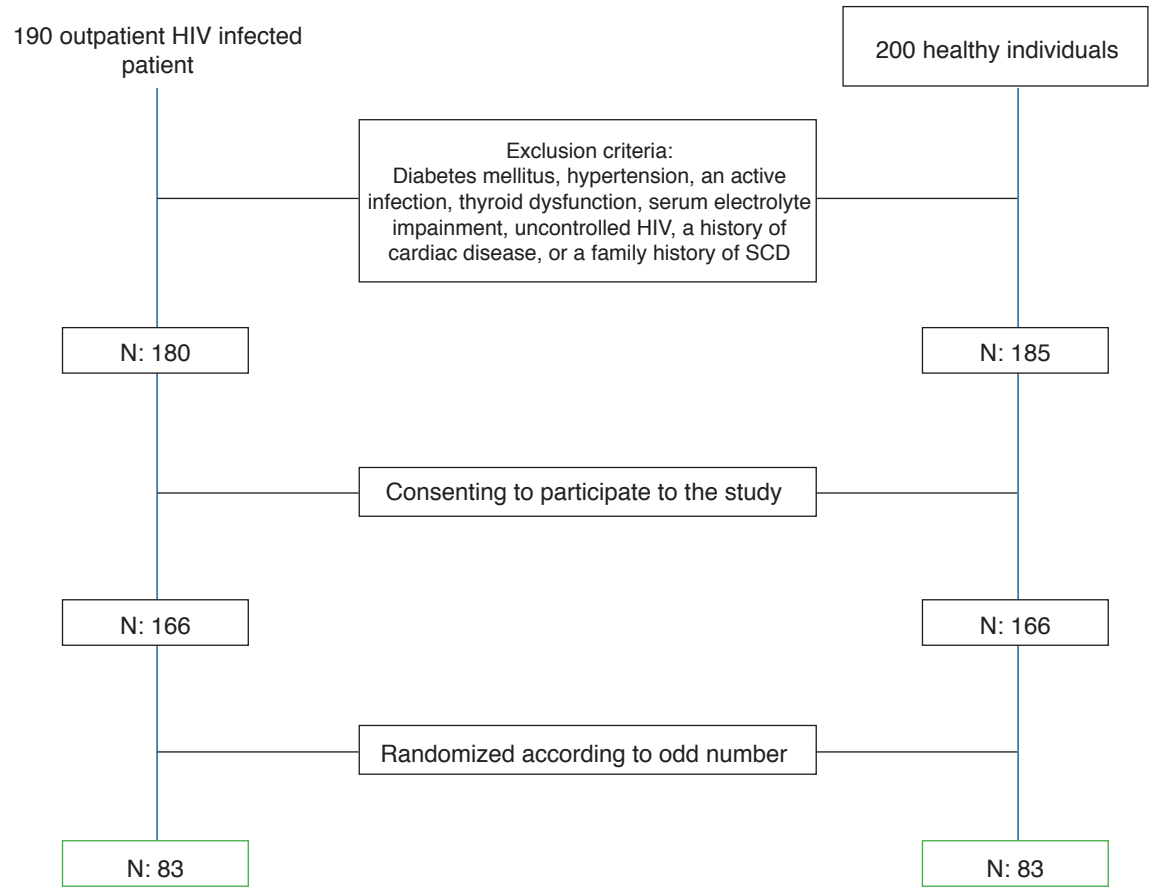

Figure 1. Volunteer enrollment and study scheme. HIV: human immunodeficiency virus; N: number; SCD: sudden cardiac death.

astolic dimensions, interventricular septum, and left ventricular posterior wall thickness were measured using the M-mode method in the parasternal long-axis view. The tricuspid annular plane systolic excursion was measured in the apical 4-chamber image through an M-mode measurement of the space between the lateral tricuspid annulus and the apex. The peak velocity of the early (E) and peak velocity of the late (A) diastoles were. Tissue Doppler velocity was measured during early diastole (E′) at the lateral corners of the mitral annulus from the apical 4-chamber view. The E:A and E:E′ ratios were calculated. The left ventricular mass (LVM) was calculated using the Devereux formula.[15] The LVM index was obtained by dividing the LVM by the body surface area.

Laboratory analysis

Biochemical analyses (hemogram, fasting blood glucose, calcium, potassium, magnesium, low-density lipoprotein [LDL], high-density lipoprotein, triglycerides, and thyroid-stimulating hormone [TSH]) were performed after the participants had fasted for 12 hours. Hemograms, biochemistry, and TSH were analyzed bythe impedance, photometric, and immunoassay methods, respectively. HIV was determined by an enzyme-linked immunosorbent assay, and positive results were confirmed bywestern blot analysis of blood specimens. HIV ribonucleic acid was measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Molecular Systems; Branchburg, NJ, USA). These values were based on the patients' values at the time of their enrollment. Values below 50 copies/mL were considered HIV under control, whereas values ≥50 copies/mL were considered uncontrolled HIV. The CD4 and CD8 T-cell counts were calculated using a FACScanflow cytometer (Becton Dickinson, San Jose, CA, USA). The lowest CD4 T-cell count measured in the patients' blood samples

Table 1. Demographic, clinical, and laboratory parameters of the study population

	ART (+) (n=83)	Controls (n=83)	*p*
Age (years)	39.55±10.41	36.82±11.16	0.963
Male, n (%)	79 (95.2)	79 (95.2)	1.000
BMI (kg/m^2)	25.46±2.95	25.38±2.79	0.855
Smoking, n (%)	47 (56.6)	36 (43.4)	0.120
Systolic blood pressure (mm Hg)	112.59±12.77	110.84±10.18	0.331
Diastolic blood pressure (mm Hg)	69.28±7.62	68.55±7.87	0.548
Fasting glucose (mg/dL)	87.93±8.65	89.40±8.13	0.265
LDL cholesterol (mg/dL)	118.73±38.92	109.51±35.08	0.123
Triglycerides (mg/dL)	120.50 (75.75-168.75)	128.00 (82.30-196)	0.319
TSH (mU/L)	1.72 (1.12-2.25)	1.56 (1.13-2.33)	0.498
Calcium (mg/dL)	9.47 (9.27-9.72)	9.45 (9.26-9.80)	0.971
Potassium (mmol/L)	4.5 (4.30-4.80)	4.5 (4.20-4.60)	0.236
Magnesium (mg/dL)	1.94 (1.91-2.11)	1.93 (1.86-2.02)	0.906

ART: Antiretroviral treatment; BMI: Body mass index; HIV: Human immunodeficiency virus; LDL: Low-density lipoprotein; TSH: Thyroid-stimulating hormone.

was considered the nadir CD4 count. The patients' first immunological parameters after diagnosis were used to calculate the CD4:CD8 ratio.

Statistical analysis

Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis. Homogeneity of sample distribution was assessed with the Kolmogorov–Smirnov test. Comparisons of continuous variables between the 2 groups were performed using the independent samples *t*-test or the Mann–Whitney U test. Normal distributions were expressed as means±standard deviations, and non-normal distributions were expressed as median values. Categorical data were compared with-chi-square test or Fischer's exact test and reported as percentages. A p value <0.05 was considered statistically significant. Spearman's or Pearson's correlation coefficient was used to assess the relationships between continuous variables. Linear regression analysis could not be performed with the Tp-e interval because the CD4:CD8 ratio was not normally distributed. For this reason, multivariate linear regression analysis was performed using age, E:A ratio, LVEF, and nadir CD4 T-cell count. In the unadjusted effects model, parameters (age, E:A ratio, LVEF, and nadir CD4 T-cell count) were compared separately, whereas in the adjusted effects model, they were compared with each other and with Tp-e interval. Coefficient of variation analyses were performed to verify intra and interobserver reproducibility for ECGs. The power of the study was 91%, and the standard effect size was 0.52%.

Table 2. Laboratory parameters of patients with HIV

Parameters	ART (+) (n=83)
Nadir CD4 T-cell counts (cell/mm^3)	362±153.97
Basal CD4:CD8 ratio	0.85
Living with HIV (month)	24
Duration of ART use (month)	12
Protease inhibitor use, n (%)	11 (13.3)
NNRTI use, n (%)	4 (4.8)
Integrase inhibitor use, n (%)	68 (81.9)

ART: Antiretroviral therapy; HIV: Human immunodeficiency virus; NNRTI: Non-nucleoside reverse transcriptase inhibitor.

RESULTS

The demographic, clinical, and laboratory parameters of the study population are presented in Table 1. The basic characteristic parameters were similar.

Laboratory parameters of patients with HIV are presented in Table 2. The mean CD4 T-cell count was 362 cells/cm^3, and the median CD4:CD8 ratio was 0.85. Of the 83 patients, 13% were using protease inhibitors.

The echocardiographic and electrocardiographic parameters of the study population are shown in Table 3. No statistically significant difference in QTc interval was observed between the 2 groups, although the QTc interval was longer in patients infected with HIV. However, the Tp-e interval was significantly longer (p=0.001), and the Tp-e:QTand Tp-e:QTc ratios were significantly higher in patients infected with HIV (p=0.002 and p=0.045, respectively).

The linear regression analysis results for the Tp-e intervalare shown in Table 4. The nadir CD4

count was an independent predictor of Tp-einterval (p=0.014, β= –0.28).

Correlation analysis of Tp-e interval and Tp-e:QT ratio with nadir CD4 levels and CD4:CD8 ratiois shown in Fig. 2.

DISCUSSION

The main findings of this study are as follows: (1) Tp-e interval, an indicator of ventricular repolarization, was found to be prolonged in patients infected with HIV; (2) a negative correlation of Tp-e interval and Tp-e:QT ratio with nadir CD4 T-cell count and CD4:CD8 ratio was found; and (3) nadir CD4 count was found to be an independent predictor of Tp-e interval.

Table 3. Echocardiographic and electrocardiographic parameters of both groups

Parameters	ART (+) (n=83)	Controls (n=83)	*p*
LVEDd (mm)	48.57±3.75	49.01±3.55	0.457
IVS (mm)	8.80±1.24	8.92±1.35	0.561
LVPW (mm)	8.75±1.18	8.81±1.19	0.719
TAPSE (mm)	21.16±2.19	21.37±1.94	0.438
E velocity(mm/s)	81.33±14.59	83.69±14.10	0.293
E:A ratio	1.18±0.33	1.22±0.29	0.362
E:E’	6.25±1.72	6.32±1.46	0.786
LVEF (%)	59.33±2.58	60.04±2.50	0.071
LV mass index (g/m^2)	75.60±16.25	78.75±16.06	0.212
Resting heart rate (bpm)	77.31±11.68	74.13±12.75	0.096
QTc interval (ms)	405.52±19.39	399.51±20.15	0.052
Tp-e interval (ms)	83.44±8.89	79.19±7.52	0.001
Tp-e:QT ratio	0.23±0.025	0.22±0.025	0.002
Tp-e:QTcratio	0.21±0.02	0.20±0.02	0.045

A: Peak velocity of late; ART: Antiretroviral therapy; E: Peak velocity of early; E′: Early diastolic velocity; HIV: Human immunodeficiency virus; IVS: Interventricular septum; LV: Left ventricle; LVEDd: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LVPW: Left ventricular posterior wall; QTc: Corrected QT interval; TAPSE: Tricuspid annular plane systolic excursion; Tp-e: T peak to Tend interval.

SCD is one of the causes of death in patients infected with HIV.[16] Although the causes of SCD in these patients are not fully understood, CVDs are generally thought to be responsible.[3] It has been shown that CVDs are more common in patients infected with HIV receiving ART than in HIV-negative individuals.[2] HIV-related chronic inflammation and the metabolic side effects of ART may result in an increased rate of CVDs in this patient group, eventually leading to SCD.[17] The findings of this study are in line with those of studies suggesting that CD4:CD8 ratio isassociated with an increase in non-AIDS–related diseases, such as CVDs, in patients infected with HIV[6] and that a low CD4 T-cell count is associated with an increased risk of CVD.[18]

Global longitudinal strain (GLS) has been shown to be associated with SCD.[19] In our previous study, we found GLS and subclinical myocardial dysfunction in patients infected with HIV, although LVEF appeared to be normal.[20] In an animal experiment, HIV infections lead to acquired sodium and potassium channelopathy.[21] Furthermore, HIV can cause ventricular arrhythmias through ventricular repolarization.[22] QTc and QT dispersions have been found to be prolonged in patients infected with HIV compared with the dispersions found in healthy individuals.[12] In our study, QTc and QT dispersions were similarly found to be more prolonged in patients infected with HIV than in healthy controls, although the difference was not statistically significant.This may be attributed to the fact that almost all the patients in our

Table 4. Adjusted and unadjusted linear regression analysis for Tp-e

	Unadjusted		Adjusted for age, E:A ratio, and LVEF	
Variables	β (95% CI)	*p*	β (95% CI)	*p*
Nadir CD4 T-cellcounts	-0.015 (-0.027 to -0.002)	0.021	-0.029 (-0.03 to -0.003)	0.014
LVEF	0.12 (-0.40 to 1.21)	0.322		
Age	0.08 (-0.16 to 0.30)	0.535		
E:A ratio	0.16 (-1.683 to 10.487)	0.154		

A: Peak velocity of late; CI: Confidence interval; E: Peak velocity of early; LVEF: Left ventricular ejection fraction; Tp-e: T peak to Tend interval.

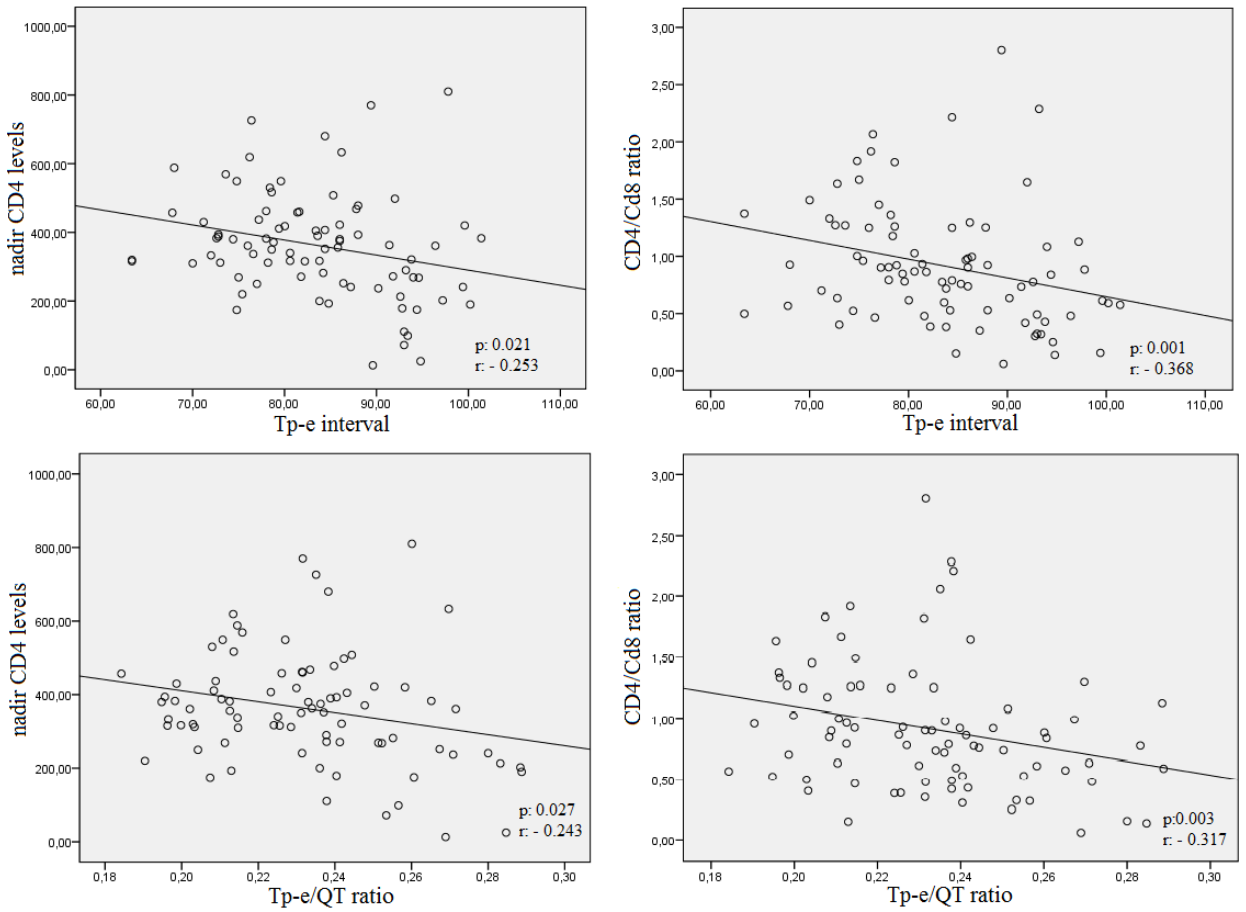

Figure 2. Correlation analysis of Tp-e interval and Tp-e:QT ratio with nadir CD4 levels and CD4:CD8 ratio.

study were receiving new-generation ART. Simpson et al.[23] reported that SCD was associated with drugs that prolong the QT interval; however, they found that SCD was related to factors other than arrhythmias. In our study, patients were not using drugs that prolong the QT interval.

Protease inhibitors have not been found to cause QTc prolongation.[24] However, owing to their metabolic side effects, the frequency of myocardial infarctions is known to be higher.[25] In our study, the Tp-e interval in patients who were using protease inhibitors was longer than in those who were not. However, owing to our small sample size, we cannot ascertain that protease inhibitors are the direct cause of Tp-e interval prolongation. It has also been shown that electrolyte imbalance predisposes to cardiac arrhythmias.[26,27] However, in our study, electrolyte imbalance was similar in the group with HIV and the control group.

New markers are needed to detect and evaluate SCD in patients infected with HIV. ECG is an effective, easily accessible, and feasible tool for predicting ventricular arrhythmias and SCD.[28] It is understood that Tp-e is an ECG interval that increases the dispersion of ventricular repolarization.[29] A prolonged Tp-e interval and increase in Tp-e:QT ratio are associated with ventricular arrhythmias (e.g., VT and VF). It has also been associated with SCD in channelopathies, myocardial infarction, and cardiomyopathies.[9–11] In this study, prolonged Tp-e intervals and Tp-e:QT and Tp-e:QTc ratios were observed in patients infected with HIV, which may suggest an increased risk of ventricular repolarization and SCD. Furthermore, Tp-e interval prolongation and increased Tp-e:QT ratio correlated with a decrease in the CD4 count and in CD4:CD8 ratio. The incidence of SCD associated with the dispersion of ventricular repolarization may be higher in patients infected with HIV, particularly in those with a low CD4 count and CD4:CD8 ratio.

Limitations

This study has some limitations. First, inflammatory markers could not be investigated. Second, the participants were not followed up with respect to SCD. Third, although no myocardial dysfunctions were observed through LVEF assessment, the patients were not evaluated in terms of subclinical myocardial dysfunction. Fourth, this was a single-center study that included relatively few patients. Finally, CD4 and CD8 counts can only be considered in patients infected with HIV.

Conclusion

This study showed that there is a prolonged Tp-e interval and increased Tp-e:QT and Tp-e:QTc ratios in patients infected with HIV. In these patients, CD4 count and CD4:CD8 ratio negatively correlate with the Tp-e interval and Tp-e:QT ratio. In patients infected with HIV, particularly in those with a low CD4 count and CD4:CD8 ratio, the dispersion of ventricular repolarization may be increased. Therefore, more attention should be paid to these patients owing to a high risk of SCD.

Ethics Committee Approval: Ethics committee approval for this study was received from the Clinical Research Ethics Committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (Approval Date: December 26, 2019; Approval Number: 065).

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Authorship contributions: Concept - Ş.Ç.; Design - A.Ş.Ç., E.A., A.B.; Supervision - Ş.Ç., A.Ş.Ç., E.A., A.B.; Materials - Ş.Ç.; Data Collection and/or Processing - Ş.Ç.; Analysis - Ş.Ç.; Literature Search - E.A.; Writing - Ş.Ç., A.Ş.Ç., E.A., A.B.; Critical Revision - Ş.Ç., A.Ş.Ç., E.A., A.B.

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Keywords: HIV; CD4; CD8; Tp-e; Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio

Anahtar Kelimeler: HIV; CD4; CD8; Tp-e intervali; Tp-e/QT oranı; Tp-e/QTc oranı