



Original Research

Evaluation of Relationship between fQRS and CD4/CD8 Ratio in Patients with HIV

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Abstract

Objectives: Myocardial dysfunction is an important cause of morbidity in human immunodeficiency virus (HIV)-infected patients. Decline in CD4 T-cell level and reversal of CD4/CD8 ratio was associated with cardiovascular events. Fragmented QRS (fQRS) can show myocardial dysfunction and cardiovascular events. The aim of this study is to investigate the presence of fQRS in HIV-infected patients and the factors affecting it.

Methods: This case-control study included 153 outpatient HIV patients (97% male) and 141 healthy subjects (96% male). Patients with cardiac disease history, arrhythmia, diabetes, cancer disease, and thyroid dysfunction were excluded from the study. Electrocardiogram, echocardiography, and biochemistry tests were performed to all participants. CD4 and CD8 T cell count, and HIV RNA level were measured in HIV-infected patients.

Results: Both groups had similar basal characteristics. Mean CD4 T-cell level was 356 cell/cm³, HIV was under control in 48%, and the rate of antiretroviral treatment use was 64%. HIV-infected patients had lower left ventricular ejection fraction (LVEF), higher Tei index, and more fQRS. HIV-infected patients with fQRS had lower nadir CD4 T-cell levels, lower CD4/CD8 ratio, and higher Tie index. In multivariate analysis, CD4/CD8 ratio and LVEF were found to be independent predictors of fQRS in HIV-infected patients.

Conclusion: Myocardial dysfunction can be seen in HIV-infected patients. Caution should be exercised in terms of myocardial dysfunction in HIV-infected patients with low CD4/CD8 ratio.

Keywords: CD4/CD8 ratio, fragmented QRS, HIV.

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With highly active antiretroviral therapy (HAART), deaths due to acquired immunodeficiency syndrome (AIDS) have decreased in human immunodeficiency virus (HIV)-infected patients and life expectancy has approached that of healthy individuals.^[1] With the extension of lifespan, the importance of heart diseases such as heart failure, myocardial dysfunction, and coronary artery disease has

increased.^[2] Although the etiology of myocardial dysfunction in HIV-infected patients is not fully known, it is thought to be caused by direct effect of HIV on myocardial tissue, by immune dysfunction, inflammation, and by drug side effects.^[3] Low CD4 T-cell level has been associated with increased cardiovascular disease risk.^[4] In addition, low CD4/CD8 ratio is one of the strong indicators of immunodeficiency.

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ciency and is associated with non-AIDS-related events.^[5] In the previous studies, the presence of myocardial fibrosis was detected in HIV-infected patients.^[6]

Fragmented QRS (fQRS) complex, which is one of the indicators of myocardial fibrosis, appears as the presence of R' wave or notching in the QRS complex in two consecutive derivations, corresponding to major coronary arteries in the electrocardiography (ECG).^[7] The presence of fQRS is thought to occur due to myocardial scar and fibrosis due to various reasons.^[8] In the previous studies, the presence of fQRS in ECG has been associated with an increase in cardiovascular events, cardiac death, and hospitalization due to heart failure.^[7,9]

Tei index shows systolic and diastolic dysfunction. Our aim in this study is to show myocardial dysfunction in HIV-infected patients with Tei index and to investigate the factors affecting fQRS.

Methods

Study Population

In this single-center case-control study, HIV-infected patients with outpatient follow-up and healthy volunteers were included in the study. Volunteers aged 18-60 were included in the study. Healthy volunteers were formed from those who applied to our hospital's occupational health unit and who did not have any disease. Patients with hypertension, diabetes, renal failure, history of cardiovascular disease (coronary artery disease and cerebrovascular accident), atrioventricular conduction disorders, atrial fibrillation and flutter, presence of pacemaker, heart failure (EF <50%), malignancy, non-HIV active infection, and thyroid disorders have been excluded from the study. Physical examination was performed; systolic and diastolic blood pressure was measured. After obtaining approval from the local ethics committee with file number 1378 on January 24, 2017, the study was initiated according to the Declaration of Helsinki. Written consent was obtained from all participants.

ECG Assessment

Twelve-channel ECG was evaluated without knowing the subgroups of the participants. The ECG was performed as paper speed 50 mm/s, the filter frequency 0.5-100 Hz, the AC filter 60 Hz, and the amplitude 10 mm/mV. fQRS was considered as an additional R wave (R') or notching in R or S wave in two consecutive derivations, feeding large coronary arteries, in the normal QRS interval.^[7] Participants were divided into two groups according to whether there is fQRS in the ECG or not.

Echocardiographic Assessment

A Philips Epiq 7 (Medical Healthcare Inc. Andover, MA, USA) ultrasound machine and a S.5-1 (1.6-3.2 mHz) probe were used for echocardiographic examination. M-mode, tissue Doppler, color Doppler, and two-, three-, and four-space images were recorded. During the recording, a single-channel ECG was recorded and an average of three beats of images was recorded. The diameter of the cardiac chambers and myocardial wall thickness was measured in the parasternal long axis. Mitral early peak velocity (E) and late velocity (A) were measured in apical four chambers, and the E/A ratio was obtained by dividing the E-velocity by the A-velocity. Tissue Doppler measurements were made in four apical chambers from the lateral annulus of the mitral valve. The left ventricular ejection fraction (LVEF) was measured in apical four chambers using the modified Simpson method. Myocardial performance index (MPI or Tei index) was obtained by dividing the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) by ejection time (ET) $([IVCT+IVRT]/ET)$.^[10] The left ventricular mass (LVM) was calculated according to the Devereux formula.^[11] The left ventricular mass index (LVMI) was obtained by dividing LVM by body surface area. All echocardiographic examinations were performed according to the European Society of Cardiology Guidelines.^[12]

Laboratory Review

A complete blood count, fasting blood glucose, urea, creatinine, low-density cholesterol, high-density cholesterol, triglyceride, thyroid-stimulating hormone (TSH), CD4 and CD8 T lymphocytes levels, and HIV-RNA were analyzed. Biochemical examinations were performed using photometric, hemogram impedance, and TSH immunoassay methods. HIV was detected by enzyme-linked immunosorbent assay test and confirmed by Western blot test. CD4 and CD8 T-cell counts were calculated by flow cytometer (FacScan flow cytometer, Becton Dickinson, San Jose, CA, USA) method. Nadir CD4 T-cell count was considered the lowest CD4 T-cell count of all time. The CD4/CD8 ratio was taken into account when the HIV diagnosis was made and was obtained by dividing the CD4 T-cell count cells (CD4/CD8). HIV ribonucleic acid (HIV RNA) was evaluated with the COBAS AmpliPrep/COBAS TaqMan HIV-1 (Roche Molecular Systems, Branchburg, USA) test. HIV RNA level of 50 copies/ml or less after initiation of antiretroviral therapy (ART) was considered as under control HIV.

Statistical Methods

The statistics of the study was analyzed using SPSS 16 software (SPSS Inc., Chicago, Illinois). Homogeneous distributions were reported as mean±standard deviation (SD).

Non-numeric data were recorded as percentages. Homogeneous distribution analysis was performed by Kolmogorov-Smirnov test. Numerical data were evaluated using independent samples t-test and Mann-Whitney U-test. Categorical data were reported using the Chi-square and Fisher's exact test. $P < 0.05$ was considered statistically significant. Univariate logistic regression analysis was performed for age, body mass index, smoking status, substance abuse, creatinine, nadir CD4 T-cell count, CD4/CD8 ratio, under control HIV, ART use, protease inhibitor use, LVEF, LVMI, and E/A ratio. Due to the small number of patients using protease inhibitors, it was not included in the multivariate analysis.

Results

Demographic and clinical parameters of HIV-infected patients and healthy individuals are shown in Table 1. There was no difference in basic characteristics in both groups. Creatinine level was higher in HIV (+) group ($p=0.029$). The mean nadir CD4 T-cell count was 356 cell/cm³. ART use rate was 64%, and it was 48% in under control HIV.

Table 2 shows echocardiographic and ECG parameters belonging to the whole population. Interventricular septum (IVS) and LVMI were higher in healthy individuals than HIV-infected patients ($p=0.035$ and $p=0.040$, respectively). IVS and LVMI values were higher in healthy subjects compared to HIV-infected patients ($p=0.035$ and $p=0.040$, respectively). E/A ratio and LVEF were lower in HIV (+) patients ($p=0.041$ and $p=0.001$, respectively). Tei index was higher in HIV (+) patients ($p < 0.001$) and fQRS was higher in HIV (+) patients ($p=0.004$).

In Table 3, HIV-infected patients were classified according to whether they had fQRS or not. Patients with fQRS were found to have lower LVEF and lower nadir CD4 T-cell count and higher Tei index ($p=0.015$, $p=0.018$, and $p=0.002$, respectively). fQRS was seen with a higher rate in those using protease inhibitors and less in those using integrase inhibitors ($p=0.072$ and $p=0.036$, respectively).

Table 4 shows univariate and multivariate analysis for fQRS as an independent indicator in HIV-infected patients. Nadir CD4 T-cell count and protease inhibitors were found as parameters affecting the development of fQRS in HIV-infected patients. CD4/CD8 ratio and LVEF were determined as independent indicators for showing fQRS in HIV-infected patients ($p=0.035$, OR: 0.34 [0.12-0.93], respectively).

Figure 1 shows fQRS findings in two different ECGs. Both ECGs were recorded at a speed of 50 mm/s.

Discussion

Our main findings in this study are as follows: (1) The frequency of fQRS in ECG was found to be higher in HIV-infected

Table 1. Demographic, clinical, and laboratory parameters in HIV-infected patients and healthy individuals

	HIV (+) (n=153)	HIV (-) (n=141)	p
Age (years)	36.77±10.25	36.82±11.16	0.963
Male gender, n (%)	148 (97)	136 (96)	0.573
BMI (kg/m ²)	24.79±2.6	25.33±2.73	0.085
Smoking status, n (%)	86 (56)	64 (45)	0.08
Systolic blood pressure (mmHg)	109.64±12.95	108.51±10.23	0.410
Diastolic blood pressure (mmHg)	67.12±8.33	66.31±7.88	0.392
Fasting glucose (mg/dL)	87.77±8.32	88.16±9.60	0.711
Creatinine (mg/dL)	0.92±0.13	0.88±0.12	0.029
LDL cholesterol (mg/dL)	111.13±34.58	107.95±32.42	0.431
Nadir CD4 T-cell count (cell/cm ³)	356	-	NA
HIV under control, n (%)	74 (48)	-	NA
Life expectancy with HIV (months)	19	-	NA
ART use, n (%)	98 (64)	-	NA
ART use time (months)	10	-	NA
Protease inhibitor use, n (%)	11 (7)	-	NA
NNRTI use, n (%)	4 (3)	-	NA
Integrase use, n (%)	83 (54)	-	NA

HIV: Human immunodeficiency virus; BMI: Body mass index; LDL: Low-density lipoprotein lipase; CD: Cluster differentiation; ART: Antiretroviral therapy; NNRTI: Non-nucleoside reverse transcriptase inhibitor.

Table 2. Echocardiographic and electrocardiographic parameters in HIV-infected patients and healthy individuals

	HIV (+) (n=153)	HIV (-) (n=141)	p
LVEDd (mm)	48.79±3.64	49.09±3.43	0.468
IVS (mm)	8.61±1.23	8.93±1.34	0.035
LVPW (mm)	8.60±1.21	8.87±1.20	0.062
LVMI (g/m ²)	75.41±15.79	78.86±15.37	0.040
TAPSE (mm)	21.43±2.04	21.45±1.89	0.933
E velocity (mm/s)	81.18±13.98	84.11±14.36	0.079
E/A ratio	1.20±0.31	1.27±0.30	0.041
LVEF (%)	59.33±2.55	60.34±2.45	0.001
Left atrium volume (mm ³)	28.63±6.53	30.16±8.35	0.083
Tei index	0.49±0.05	0.47±0.05	<0.001
fQRS, n (%)	38 (25)	16 (11.3)	0.004

HIV: Human immunodeficiency virus; LVEDd: Left ventricular end-diastolic diameter; IVS: Interventricular septum; LVPW: Left ventricular posterior wall; LVMI: Left ventricular mass index; TAPSE: Tricuspid annular plane systolic excursion; E: Early peak velocity; A: Late peak velocity; LVEF: Left ventricular ejection fraction; fQRS: Fragmented QRS.

patients; (2) the nadir CD4 (+) T lymphocyte count was found to be lower in HIV-infected patients with fQRS on

Table 3. Demographic, clinical, laboratory, and echocardiographic parameters in HIV-infected patients

	fQRS (+) (n=38)	fQRS (-) (n=115)	p
Age (years)	37.86±10.62	36.42±10.15	0.463
BMI (kg/m ²)	25.30±2.91	24.62±2.54	0.170
Systolic blood pressure (mmHg)	111.71±12.75	108.96±13.00	0.257
Diastolic blood pressure (mmHg)	67.76±8.60	66.91±8.26	0.587
Smoking status n (%)	21 (55)	65 (57)	0.893
Substance abuse n (%)	5 (13)	12 (10)	0.766
LVEF (%)	59.04±2.47	60.19±2.59	0.015
LVMI (g/m ²)	78.84±17.95	74.26±14.91	0.122
E velocity (mm/s)	82.46±12.48	80.75±14.62	0.515
A velocity (mm/s)	66.81±15.72	70.20±15.48	0.285
E/A ratio	1.26±0.29	1.18±0.31	0.155
Tei index	0.50±0.06	0.48±0.05	0.002
ART use n (%)	20 (54.1)	78 (67.8)	0.167
Under control HIV, n (%)	16 (42)	63 (55)	0.194
Nadir CD4 T-cell count (cell/cm ³)	295	361	0.042
CD4/CD8 ratio	0.50	0.76	0.018
Protease inhibitor use, n (%)	6 (16.2)	6 (5.2)	0.072
NNRTI use, n (%)	0 (0)	4 (3.5)	0.573
Integrase inhibitor use, n (%)	14 (37.8)	68 (59.1)	0.036

HIV: Human immunodeficiency virus; BMI: Body mass index; LVEF: Left ventricular ejection fraction; E: Early peak velocity; A: Late peak velocity; ART: Anti-retroviral treatment; CD: Cluster differentiation; NNRTI: Non-nucleoside reverse transcriptase inhibitor; fQRS: Fragmented QRS.

their ECG; (3) univariate and multivariate analysis showed that CD4 T-cell count in HIV-infected patients was a non-independent parameter affecting the development of fQRS; (4) CD4/CD8 ratio was lower in those with fQRS detected on ECG; (5) in multivariate analysis, CD4/CD8 ratio was found to be an independent predictor of fQRS in HIV-infected patients. To the best of our knowledge, this is the first study to evaluate the presence of fQRS in HIV-infected patients.

Coronary artery disease, cerebrovascular diseases, and HIV-related cardiomyopathy have become chronic problems with the prolongation of life expectancy in HIV-infected patients during the HAART period.^[13-15] Several mechanisms have been suggested for the development of myocardial dysfunction in HIV-infected patients. These mechanisms are thought to be the direct myocardial effect of HIV, chronic inflammation, autoimmunity, and side effects of ART.^[3] In a previous study, HIV invasion was detected in the left ventricular myocardial tissue in postmortem examination of HIV-infected adult patients.^[16] In addition, it has been shown that pro-inflammatory cytokines, es-

Table 4. Univariate and multivariate analysis to show fQRS in HIV-infected patients

	Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	p	Odds ratio (95 % CI)	p
Age	1.02 (0.99-1.04)	0.278		
BMI	1.02 (0.92-1.14)	0.718		
Smoking status	1.37 (0.75-2.49)	0.300		
Substance abuse	1.94 (0.65-5.76)	0.233		
Creatinine	4.31 (0.42-44.70)	0.221		
Nadir CD4 T-cell count	1.0 (0.99-1.0)	0.069		
CD4/CD8 ratio	0.28 (0.11-0.75)	0.012	0.34 (0.13-0.91)	0.032
Under control HIV	1.59 (0.75-3.34)	0.224		
ART use	0.56 (0.26-1.19)	0.130		
Protease inhibitor	3.52 (1.06-11.67)	0.040		
LVEF	1.03 (0.91-1.15)	0.653		
LVMI index	1.01 (0.99-1.03)	0.443		
E/A ratio	1.68 (0.64-4.37)	0.291		

CI: Confidence interval; HIV: Human immunodeficiency virus; fQRS: Fragmented QRS; BMI: Body mass index; CD: Cluster differentiation; ART: Antiretroviral therapy; LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index; E: Early peak velocity; A: Late peak velocity.

pecially inflammatory markers such as interleukin-1 beta and tumor necrosis factor, increase in these patients.^[17] Fiala et al.^[18] detected HIV invasion in inflammatory cells, macrophages, and T lymphocytes in the heart tissue with the polymerase chain reaction method in their postmortem study, and found that macrophage activation and viral products induced apoptosis of cardiomyocytes with hybridization techniques. In an experimental study, it was observed that CD4 T-cells had a positive effect on myocardial recovery in mice with myocardial infarction.^[19] Low CD4 T levels have been associated with worsening of heart failure and cardiovascular events.^[4] High CD8 T-cell level contributes to the development of immune deficiency by increasing PD-1 release.^[20] Serrano-Villar et al.^[5] showed in their case-control study that low CD4/CD8 ratio is an independent risk factor in predicting non-AIDS-related morbidity and mortality. High CD8 T-cell level (low CD4/CD8 ratio) may predispose to cardiovascular events by causing chronic inflammation.^[21] Thiara et al.^[6] compared HIV-infected patients with healthy individuals without cardiovascular disease by cardiac magnetic resonance imaging and found increased myocardial fibrosis in infected patients during the HAART period.

fQRS, which is an inexpensive and easily accessible marker to show myocardial fibrosis, is seen as notching in the QRS wave and an additional R wave in the ECG.^[22] The pres-

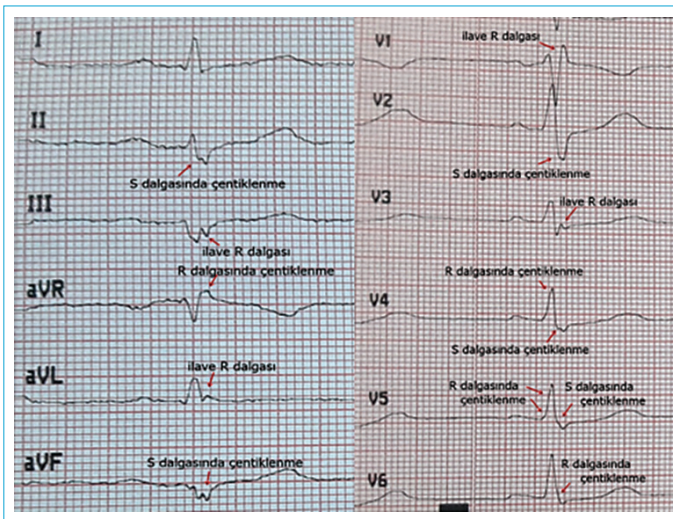


Figure 1. The various types of fQRS in ECG.

ence of fQRS on the ECG has been found to be associated with diseases such as myocardial infarction, non-ischemic dilated cardiomyopathy, arrhythmias, cardiac sarcoidosis, diabetic microalbuminuria, and chronic renal failure.^[7,23-25] In patients with a history of myocardial infarction, the sensitivity of fQRS in showing myocardial scar tissue in myocardial perfusion scintigraphy was found to be 75% and specificity as 81%.^[26] fQRS was found around 60% in patients with chronic renal failure with preserved LVEF, and MPI (Tei index), which reflects left ventricular systolic and diastolic function, was found to be higher in patients with fQRS.^[27] In our study, fQRS was detected in around 38% of HIV-infected patients. In addition, a higher Tei index was found in patients with fQRS. Onoue et al.^[28] investigated the presence of fQRS in patients with heart failure with preserved ejection fraction (EF), and patients with fQRS on the ECG were found to have more heart failure findings, higher high sensitive troponin T, and brain natriuretic peptide (BNP) levels. fQRS and plasma BNP levels were determined to be independent predictors for demonstrating heart failure with preserved EF.

Tei index is a reliable parameter to show systolic and diastolic dysfunction measured with echocardiography. It is not affected by systolic and diastolic blood pressure, heart rate, valve insufficiencies, and anterior and posterior cardiac load.^[29] In our study, a high Tei index was found in patients with fQRS.

In this study, fQRS presence was detected with higher rates in HIV-infected patients, than in healthy individuals. In addition, higher Tei index and lower CD4/CD8 ratio were found in HIV-infected patients with fQRS. In general, myocardial inflammation has been found in HIV-infected patients and HIV-infected patients with a low CD4/CD8 ratio.^[6,21] Myocardial fibrosis and fQRS may have occurred secondary to

myocardial inflammation. In addition, myocardial inflammation and fibrosis may have caused myocardial dysfunction (high Tei index). In this study, a severe relationship was found between fQRS and Tei index. Particular attention should be paid to myocardial dysfunction in HIV-infected patients with a low CD4/CD8 ratio in the presence of fQRS in the ECG. There is a need for large-scale studies on this topic.

Limitations

Not using biochemical and imaging techniques as indicators of myocardial fibrosis can be seen as a limitation. Second, it can be said that patients did not have follow-up. The low number of patients can be said as another limitation.

Conclusion

CD4/C8 ratio was found to be an independent predictor in showing fQRS, which is an indicator of myocardial dysfunction in HIV-infected patients. Care should be taken in terms of myocardial dysfunction in HIV-infected patients, especially in those with a low CD4/CD8 ratio, in the presence of fQRS in the ECG.

Disclosures

Ethics Committee Approval: This study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (24.01.2017/1378).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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