ORIGINAL ARTICLE

QT Dispersion in HIV-Infected Patients Receiving Combined Antiretroviral Therapy

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Background: A higher prevalence of QT prolongation has been reported among human immunodeficiency virus (HIV)-infected patients. Previous studies have demonstrated that QT dispersion is a better predictor of serious ventricular tachyarrhythmia and cardiac mortality than corrected QT (QTc) interval. However, data of QT dispersion in HIV-infected patients receiving a combined antiretroviral therapy (cART) is limited. We sought to assess QTc interval and QT dispersion in HIV-infected patients receiving cART. The association between QT parameters and heart rate variability (HRV) was also examined.

Methods: Ninety-one HIV-infected patients receiving cART (male = 33, mean age = 44 ± 10 years) and 70 HIV-seronegative subjects (male = 25, mean age = 44 ± 8 years) were enrolled in the study. In a resting 12-lead electrocardiogram, QT interval was measured by the tangent method in all leads with well-defined T waves. The QT dispersion was defined as the difference between maximum and minimum QTc intervals in any of 12 leads.

Results: The baseline characteristics were not different between the two groups. We demonstrated the significantly longer mean QTc interval (420 ± 21 vs. 409 ± 21 ms, $P < 0.001$), and greater QT dispersion in HIV-infected group compared to the control group (85 ± 29 vs. 55 ± 23 ms, $P < 0.001$). Among the HIV-infected patients, those who had lower CD4 lymphocyte count (< 350 cells/mm³) tended to have greater QT dispersion (92 ± 28 vs. 81 ± 29 ms, $P = 0.098$). There were no associations between QT parameters and either HRV or cART regimens.

Conclusions: HIV-infected patients receiving cART were associated with prolonged QTc interval and increased QT dispersion, independent of autonomic dysfunction and antiretroviral drugs, which may have led to the potentially higher risk of ventricular arrhythmia and cardiac mortality.

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antiretroviral therapy; human immunodeficiency virus; QT interval; QT dispersion

After the development of a combined antiretroviral therapy (cART), the mortality rate from infection has decreased significantly in human immunodeficiency virus (HIV)-infected patients. However, the cardiac manifestation has become the prominent cause of morbidity and mortality

in this group of patients.^{1–3} Previous studies have shown that the incidence of sudden cardiac arrest in HIV-infected patients was significantly higher than the general population with similar risk factors and contributes to most cardiac deaths in HIV-infected patients.^{4,5} Several studies have also

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demonstrated the higher prevalence of QT-interval prolongation in HIV-infected patients compared to the controls.⁶⁻⁹ Despite the association between the prolongation of the QT interval and serious ventricular tachyarrhythmia, the accumulating data have shown that the QT dispersion is a better predictor of cardiac mortality than corrected QT (QTc) interval.¹⁰⁻¹² Nevertheless, the QT dispersion has never been investigated in HIV-infected patients. Furthermore, it has been shown that the alteration of autonomic function and some antiretroviral drugs are the potential causes reported to cause QT prolongation in HIV-infected patients.^{9, 13-15} In the present study, we conducted the investigation to assess the QTc interval and QT dispersion in HIV-infected patients receiving cART compared to the controls. We also sought to examine the effects of antiretroviral drugs and the changes in cardiac autonomic function using heart rate variability (HRV) on the QTc interval and QT dispersion.

METHODS

Studied Population

The study protocol was approved by the local institutional review board, and the informed consent was obtained from all subjects enrolled in this study. Between February 2009 and June 2012, 91 HIV-infected patients (age >18 years) attending the HIV clinic at Maharaj Nakorn Chiang Mai hospital were enrolled. All HIV-infected patients had been receiving combination of at least three antiretroviral agents selected from several drug classes which included nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Patients were excluded if they had apparent heart diseases or electrolytes imbalance. None of the participants were taking any medication known to prolong the QT interval. The CD4 lymphocyte counts and HIV RNA levels were carried out in all HIV-infected patients. Seventy healthy volunteers with a negative HIV antibody test were also recruited in the study. History taking, physical examination, and 12-lead electrocardiography (HP M1700A, Hewlett Packard, Palo Alto, CA, USA) were performed.

Among 91 HIV-infected patients, 51 subjects underwent 24-hour Holter (GE Seer Light Extend, GE Medical Systems, Suzuken Company, Ltd.,

Nagoya, Aichi, Japan) monitoring for HRV assessment. Recordings lasting for ≥ 16 hours and of sufficient quality for evaluation were included in the analysis. Before analyzing the data, they were manually preprocessed.

Analysis of the Electrocardiograms (ECGs)

Twelve-lead surface ECGs were used to evaluate QT parameters. The ECGs were recorded at a paper speed of 50 mm/s. The heart rate, P-wave duration, PR interval, QRS duration, QT interval, and QTc interval were measured. The QT interval was measured in all leads from the earliest QRS deflection to the end of the T wave. The QT was corrected for heart rate using Bazett's formula ($QTc = QT/\sqrt{RR}$). QT dispersion was defined as the maximum interval minus the minimum interval measured on the ECG. The T-wave end was defined by the threshold method that localizes the T offset as an intercept of the T wave or of its derivative with a threshold above the isoelectric line. All ECGs were analyzed for ECG parameters by two blinded investigators.

Heart Rate Variability

Time-domain and frequency-domain analyses were performed according to the standard guidelines.¹⁹ Time-domain HRV indexes were analyzed using statistical methods. The square root of the mean squared differences of successive normal-to-normal (NN) intervals (rMSSD), the standard deviation (SD) of all NN intervals (SDNN), the average of the SD of the 5-minute NN intervals over the entire recording (ASDNN), and the SD of the average NN intervals calculated over 5-minute periods of the entire recording (SDANN) were measured.

Frequency-domain HRV were analyzed using autoregressive power spectral analysis applied to the RR interval time series. The following spectral bands were identified: very low frequency (VLF) (0.003–0.04 Hz), low frequency (LF) (0.04–0.15 Hz), and high frequency (HF) (0.15–0.4 Hz). Total power (0–0.5 Hz) and the areas below each peak were calculated in absolute units (ms^2).

Statistical Analysis

Results were expressed as mean $\pm$ SD, unless otherwise specified. The numerical variables were compared between groups with the Mann-Whitney

Table 1. Baseline Characteristic of the Studied Subjects

Characteristics	HIV-Infected (n = 91)	Control (n = 70)	P Value
Age (years)	44.2 ± 7.9	44.1 ± 10.2	0.957
Male	33 (36.3%)	25 (35.7%)	1.000
Body mass index (kg/m ²)	22.2 ± 2.8	23.5 ± 4.0	0.074
FBS (mg/dL)	97.0 ± 6.8	93.1 ± 11.8	0.136
Total cholesterol (mg/dL)	217.2 ± 40.2	208.5 ± 39.3	0.220
Triglyceride (mg/dL)	177.7 ± 140.5	112.3 ± 58.1	<0.001
LDL cholesterol (mg/dL)	129.6 ± 36.0	130.4 ± 80.7	0.941
HDL cholesterol (mg/dL)	53.7 ± 14.5	55.8 ± 16.6	0.461
Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.091
Potassium (mg/dL)	4.1 ± 0.4	4.4 ± 0.5	0.106
Calcium (mg/dL)	8.8 ± 0.8	9.2 ± 0.4	0.475
Magnesium (mg/dL)	1.9 ± 0.2	1.9 ± 0.1	0.811

FBG = fasting blood glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2. Electrocardiographic Variables

ECG Variables	HIV-Infected (n = 91)	Control (n = 70)	P Value
Resting heart rate (bpm)	77 ± 12	70 ± 10	<0.001
P-wave duration (ms)	87 ± 15	91 ± 15	0.062
PR interval (ms)	158 ± 22	163 ± 23	0.188
QRS duration (ms)	91 ± 72	95 ± 103	0.740
Mean QTc interval (ms)	420 ± 21	409 ± 21	0.002
QT dispersion (ms)	85 ± 29	55 ± 23	<0.001

U test. Proportions were compared by Fisher's exact test. The comparisons of QTc interval and QT dispersion between groups were adjusted according to potential confounding variables. Multivariate analyses were performed for variables with a P value <0.1 in univariate analysis using the linear regression procedure. A one-way analysis of variance was used to compare the differences between cART regimens and QT parameters. Multiple comparisons were analyzed with the Tukey test. Correlations were analyzed using nonparametric (Spearman) correlation and expressed with Spearman's rho. P values <0.05 were considered statistically significant. Statistical software package SPSS version 15.0 (Chicago, IL, USA) was used for analysis.

RESULTS

Baseline Characteristics

The baseline characteristics were comparable between HIV-infected patients and control subjects as shown in Table 1. However, the fasting

triglyceride level was significantly higher in HIV-infected patients than control subjects. Among 91 HIV-infected patients, HIV infection had been diagnosed for 4.3 ± 5.5 years at the time of study and the mean duration of cART since the diagnosis was 1.5 ± 2.0 years. The mean CD4 lymphocyte count was 440 ± 188 cells/mm³. The cART regimens consisted of efavirenz-based regimen (23%), nevirapine-based regimen (63%), and PI-based regimen (14%).

ECG Parameters

All subjects were in sinus rhythm. The mean heart rate was significantly faster in HIV-infected patients than the controls. There were no differences in P-wave duration, PR interval, and QRS duration between two groups. The mean QTc interval in HIV-infected patients receiving cART was significantly longer, and QT dispersion was also significantly greater than that of control subjects (Table 2). Among the HIV-infected patients, those who had lower CD4 lymphocyte count (<350 cells/mm³) tended to have greater QT dispersion (92 ± 28 vs. 81 ± 29 ms, $P = 0.098$).

Table 3. The Different Combination Antiretroviral Therapy Regimens and QT Parameters

QT Parameters	Combination Antiretroviral Therapy Regimens			P Value
	EFV-Based (n = 21)	NVP-Based (n = 57)	PI-Based (n = 13)	
QTc interval (ms)	421 ± 21	419 ± 21	419 ± 20	0.924
QT dispersion (ms)	88 ± 30	84 ± 29	87 ± 26	0.808

EFV = efavirenz; NVP = nevirapine; PI = protease inhibitors.

Table 4. The Correlation between Cardiac Autonomic Function and QT Parameters in HIV-Infected Patients

Parameters	Corrected QT Interval (n = 51)		QT Dispersion (n = 51)	
	Pearson Correlation	P Value	Pearson Correlation	P Value
SDNN	0.010	0.942	0.168	0.234
SDANN	−0.002	0.987	0.167	0.236
ASDNN	0.136	0.336	0.025	0.859
rMSSD	0.089	0.529	0.052	0.716
Total power	0.172	0.224	0.040	0.778
VLF power	0.175	0.216	0.023	0.872
LF power	0.181	0.198	0.150	0.289
HF power	0.087	0.538	0.046	0.785

SDNN = standard deviation (SD) of all normal-to-normal (NN) intervals; SDANN = SD of the average NN intervals calculated over 5-minute periods of the entire recording; ASDNN = average of the SD of the 5-minute NN intervals over the entire recording; rMSSD = square root of the mean squared differences of successive NN intervals; VLF = very-low-frequency; LF = low-frequency; HF = high-frequency.

Among HIV-infected patients receiving cART, we found that there was no association between cART regimens and either QTc interval or QT dispersion (Table 3). After multivariate linear regression analysis adjusted with age, gender, creatinine, triglyceride, potassium, calcium, magnesium, and cART regimens, HIV-infected patients still had significantly longer QTc interval and QT dispersion.

The Correlation between Cardiac Autonomic Function and ECG Parameters

We examined the correlation between the cardiac autonomic function and ECG parameters including heart rate, QTc interval, and QT dispersion in 51 HIV-infected patients. We demonstrated that the heart rate was inversely correlated with ASDNN ($r = -0.434$, $P = 0.001$), with total power ($r = -0.406$, $P = 0.003$), with VLF ($r = -0.469$, $P = 0.001$), and with LF ($r = -0.328$, $P = 0.019$). However, there was no correlation between heart rate and HF component. In addition, we did not find any significant correlations between cardiac autonomic function and either QTc interval or QT dispersion (Table 4).

DISCUSSION

In the present study, we demonstrated that HIV-infected patients receiving cART had a prolonged QTc interval, which is consistent with previous reports.^{6–8} Nevertheless, it has been described that QT dispersion, an index of the inhomogeneity of myocardial repolarization, is a better predictor of malignant ventricular arrhythmias and sudden cardiac death than the QTc interval.^{10–12} However, the QT dispersion has never been examined in HIV-infected patients. Our study represents the first analysis of the effect of HIV infection on the QT dispersion. We showed that QT dispersion was significantly greater in HIV-infected patients compared to the control subjects.

There are several potential causes of the prolongation of QT interval and QT dispersion in HIV-infected patients. The antiretroviral drugs have been shown to cause a prolongation of the QT interval, particularly efavirenz and PIs.^{13–15} However, in the present study, we found that neither efavirenz-based regimen nor PIs-based treatment was associated with the increase in QTc interval and QT dispersion.

We have recently demonstrated the changes of the cardiac sympathovagal balance in HIV-infected patients receiving cART.¹⁶ Consistently, in the present study, we showed that the resting heart rate was faster in HIV-infected patients which may have been due to the decrease in vagal activity. Previous small study suggested that prolonged QT interval in HIV-infected patients might have been associated with alterations in cardiac innervations as a result of autonomic neuropathy.⁹ However, we did not find the correlation between any HRV parameters and either QTc interval or QT dispersion. As a result, cardiac autonomic dysfunction may have not accounted for the alteration of QTc interval and QT dispersion in this group of patients. Furthermore, we demonstrated that HIV-infected patients with the lower CD4 lymphocyte count tended to have a greater QT dispersion. Similarly, previous study demonstrated the higher incidence of dilated cardiomyopathy among HIV-infected patients with a CD4 lymphocyte count of less than 400 cells/mm³.¹⁷ In light of these data, we postulated that the extent of immunodeficiency may influence the QT dispersion by HIV directly infecting cardiac myocytes and activating cytokines.¹⁷⁻¹⁹

Therefore, in addition to the presence of cardiac autonomic dysfunction, the prolongation of QT interval and the increase in QT dispersion demonstrated in this study may contribute significantly to the mechanism underlying sudden cardiac death in HIV-infected patients receiving cART.

The present study had some limitations. Due to the cross-sectional nature of the study, we did not have the data showing at what time point when the QT parameters started to prolong or change following HIV infection. Since we have recently published the study comparing HRV between HIV-infected patients and control subjects,¹⁶ we examined HRV only in 51 HIV-infected patients in this study. Therefore, the correlation between autonomic function and QT parameters could not be compared between the HIV-infected and control subjects. In addition, we did not observe any ventricular tachyarrhythmia in the studied population. This may be due to the relatively young age and small number of the population. Long-term study with larger population may be warranted.

CONCLUSION

HIV-infected patients receiving cART were associated with the prolongation of QTc interval and increased QT dispersion, independent of autonomic dysfunction, and antiretroviral drugs. The presence of cardiac autonomic dysfunction and the increase in QTc interval and QT dispersion may have led to the potentially higher risk of ventricular arrhythmia and cardiac mortality in this group of patients.

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