ORIGINAL ARTICLE

Cardiac Autonomic Function and QT Interval Prolongation in Human Immunodeficiency Virus Patients Treated with Protease Inhibitor

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Objective: Protease inhibitors (PIs) may impair cardiac autonomic function and conduction velocity, leading to clinical bradycardia or conduction delays. In patients with human immunodeficiency virus (HIV) receiving PI therapy, changes in 24-hour heart rate variability (HRV) are used to monitor alterations in sympathetic and parasympathetic activity. The present study investigates the differences in 24-hour HRV between patients with HIV receiving antiretroviral therapy (ART) with a PI regimen and without a PI regimen.

Materials and Methods: The authors conducted a cross-sectional analysis of participants with HIV receiving a PI regimen and a non-PI regimen. An electrocardiogram and 24-hour Holter monitoring were performed on each participant. The primary outcome is the comparison of 24-hour HRV parameters between the PI and non-PI groups. The secondary outcomes include the analysis of differences in the minimum, maximum, and mean values of 24-hour heart rate (HR) and corrected QT (QTc) interval.

Results: Thirty eligible participants (average age 44.6 years, 33% female) were enrolled in the present study. Twelve participants received a PI regimen, while 18 received a non-PI regimen. The PI group showed average values of 29.0 for rMSSD, 47.9 for SDNN, and 33.5 for the HRV triangular index. The non-PI group averaged 25.8 for rMSSD, 46.7 for SDNN, and 33.8 for the HRV triangular index. No statistically significant differences existed between the groups in any of these measures. Similarly, no significant differences were found in the 24-hour HR minimum, maximum, or mean, although the PI group tended to have slightly lower values. Interestingly, the QTc interval measures in the PI group (minimum, maximum, and mean) were slightly longer than those in non-PI group, but these differences also did not reach statistical significance.

Conclusion: The authors' study found no significant differences in 24-hour HRV between HIV-infected participants on PI regimens and those on non-PI regimens

Keywords: Antiretroviral therapy; Cardiac autonomic function; HIV; Human immunodeficiency virus (HIV); Heart rate variability; Protease inhibitors

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Since the outbreak of the HIV/AIDS epidemic, an estimated 85.6 million people have been diagnosed with the Human Immunodeficiency Virus (HIV), and around 40.4 million have died from HIV-related causes. Globally, approximately 39 million people were living with HIV at the end of 2022[1]. In Thailand, an estimated 1.1% of the population is infected. Around 65% of individuals with HIV have access to antiretroviral therapy (ART)[2]. This highly effective treatment significantly reduces mortality rates and improves life expectancy. However, both ART and HIV infection itself can increase the risk of cardiovascular diseases[3]. This risk ranges from 6.5% to 15% and is attributed to various factors, including chronic inflammation, co-infection with other opportunistic diseases, and side effects of the medication. People living with HIV are more likely to develop cardiovascular conditions, such as atherosclerotic vascular disease, heart failure, pulmonary arterial hypertension, cardiomyopathy, cardiac conduction defects, and acute myocardial infarction[3-7].

Thailand's 2017 national guidelines on HIV/AIDS

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treatment and prevention recommend Protease Inhibitors (PIs) as a first-line ART regimen. Boosted lopinavir and boosted atazanavir are among the recommended PIs[8]. However, these medications are associated with several potential side effects, including elevated cholesterol, elevated blood sugar, prolonged PR interval, and prolonged QT interval[9-11]. Studies have linked PIs to life-threatening cardiovascular complications in pediatric patients, including complete atrioventricular block, bradycardia, and cardiomyopathy[12,13]. Adult patients receiving PI therapy may experience conditions that disrupt the heart rate (HR), including sinus bradycardia, bradycardia-tachycardia syndrome, junctional bradycardia, and complete atrioventricular block[14-17]. Additionally, PI therapy in those with HIV has been linked to prolonged QRS durations on electrocardiogram (ECG). Furthermore, research suggests that PI use increases the risk of bundle branch block[11,18].

Heart rate variability (HRV) refers to the natural fluctuation between consecutive heartbeats. This measurement reflects the activity of the autonomic nervous system, which regulates heart rate. HRV can be assessed using 24-hour Holter electrocardiogram (ECG) monitoring. A higher HRV value is generally associated with dominance of the parasympathetic nervous system, which promotes relaxation. Conversely, a lower HRV value suggests an activation of the sympathetic nervous system, which is responsible for the fight-or-flight response[19,20]. Studies have shown that persistently lower HRV values are linked to an increased risk of death from myocardial infarction and diabetic neuropathy. Studies have shown that non-boosted PI regimens are associated with higher HRV than non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens. Boosted PI regimens appear to mitigate this effect[21]. A meta-analysis comparing the effects of ARV on patients with HIV and a healthy control group found lower vagal tone and increased sympathetic tone in the HIV group. This was indicated by lower standard deviations of all NN intervals (SDNN), lower root mean square of the successive differences between normal RR intervals (rMSSD), and higher low-frequency: high-frequency (LF/HF) ratio in the time domain[22]. These findings suggest that HIV itself may decrease parasympathetic activity while PI treatment increases it, potentially slowing heart rate and cardiac conduction velocity. Additionally, PI use has been associated with clinical bradycardia, which typically resolves upon discontinuation of the medication[21].

Using 24-hour Holter monitoring with HRV analysis to quantify autonomic function, the presenr study compares HRV variables and corrected QT (QTc) interval in participants with HIV receiving a PI regimen and without a PI regimen.

Materials and Methods

Study population

This cross-sectional study compared the HRV of participants with HIV receiving a PI regimen to those not on a PI regimen. Participants were recruited from an outpatient clinic at the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand. Inclusion criteria were age over 18 years, confirmed HIV infection, an undetectable viral load within 12 months of ART treatment, and maintenance of a CD4 count above 350 cells/mm^3 for at least 12 months. Patients with comorbid conditions that could affect cardiac autonomic function or conduction velocity were excluded. These excluded conditions included coronary artery disease, cardiomyopathy, thyroid dysfunction, congenital heart disease, cardiac arrhythmia, active infection, pregnancy, and the use of medications like anti-arrhythmic drugs, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, antihistamines, sulfonylureas, and insulin. All participants provided written informed consent to participation and publication. The participants were divided into two groups depending on whether they received a PI or a non-PI treatment regimen. This study was conducted following the tenets of the 2013 revision of the Declaration of Helsinki. It was approved by the Research Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA No. 058/2563).

Data collection and definition

The electronic medical records contained data on the patient's baseline characteristics and laboratory results, including HIV infection status, CD4 count, and medication. Each patient underwent a 12-lead ECG before 24-hour Holter monitoring, and the HRV data were collected using 24-hour Holter monitoring.

24-Hour Holter monitoring and HRV measurement

The present study utilized the Mortara® H3+ Digital Holter Recorder (Welch Allyn, Inc., Skaneateles Falls, NY, USA) for 24-hour Holter monitoring. After data collection, a single researcher performed manual artifact removal. The HScribe™ Holter Analysis System v.6 was then used to analyze the data. The time domain analysis variables were SDNN, rMSSD, and HRV triangular index. Additionally, the system automatically determined the mean, maximum, and minimum QTc intervals from a 12-lead ECG. Definitions of the HRV variables are provided in Table 1[20].

Endpoints

The primary outcome measure was HRV, assessed using the time-domain parameters SDNN, rMSSD, and HRV triangular index. The secondary endpoints included

Table 1. Definitions of Heart Rate Variability Variables[20]

pNN50	The percentage of successive differences in RR values greater than 50 ms (independent of sign) during the period.
RMS SD	Root mean square of the successive differences in RR values during the period.
SDNN index	The average of five-minute period standard deviations of the RR intervals during the period. Valid five-minute periods have at least two valid RR intervals, also called Magid SD.
SDANN	Standard deviation of all five-minute average RR intervals during 24 hours. Valid five-minute periods have at least two valid RR intervals, also called Magid SD.
HRV Triangular index	The total number of RR intervals during the period divided by the height of the histogram of all RR intervals measured on a discrete scale with bins of 7.8125 ms.

the mean, minimum, and maximum heart rates and the mean, minimum, and maximum QTc intervals. All information was derived from the 24-hour Holter monitoring data.

Statistical Analysis

The sample size was calculated using different means, estimating effect size (d=0.8), an α error probability of 0.1, and a power of 0.8. Using G*Power version 3.1.9.4 for the analysis, the estimated sample size was 15 participants in each group, achieving an actual power of 0.8. Categorical variables were reported as numbers and percentages and compared between groups using the Pearson Chi-square test. The continuous variables with Gaussian distribution were presented as mean ± standard deviation (SD) and compared using independent-sample t-tests. The continuous variables without Gaussian distribution were summarized as median (interquartile range [IQR]) and compared using the Kruskal-Wallis test. Statistical significance was defined as a $p<0.05$. Significant between-group differences in the endpoints were determined using independent-sample t-tests to compare the mean values between the two groups. All statistical tests were performed using SPSS v.26.0 software (SPSS Inc., Armonk, NY, USA).

Results

Patient characteristics

We enrolled a total of 30 eligible participants. The mean participant age was 44.6±9.0 years, with 33% female. PI regimens with boosted ritonavir were used by 40% (n=12) of the group, while the remaining 60% (n=18) received non-PI regimens. Within the PI regimen group, seven participants were treated with lopinavir, four with atazanavir, and one with darunavir. Comorbidities included hypercholesterolemia (n=10, treated with statins), hypertension (n=1, treated with daily amlodipine 5 mg), chronic hepatitis C (n=1, achieved sustained virologic response after treatment), and spondyloarthropathy (n=1; treated with weekly methotrexate 5 mg). A baseline 12-lead electrocardiogram revealed a single case of right bundle branch block. No other abnormalities were detected in resting ECGs. Patient variables are summarized in Table 2.

While the PI regimen group exhibited a lower body weight, the difference in body mass index was not statistically significant. Similarly, laboratory results showed lower CD4 counts and hemoglobin levels in the PI regimen group, but these variations were not statistically significant. Interestingly, 12-lead ECGs revealed a longer mean QRS duration in the PI regimen group. All other baseline characteristics were equivalent between the two groups.

24-Hour Holter monitoring analysis

24-hour Holter monitoring results analysis revealed no statistically significant differences in HRV between the PI and non-PI groups. The mean ± SD values for the rMSSD, SDNN, and HRV triangular index were 29.0±15.8 ms, 47.9±10.3 ms, and 33.5±9.2 ms, respectively, in the PI group. In the non-PI group, they were 25.8±16.8 ms, 46.7±16.2 ms, and 33.8±10.7 ms, respectively. The observed differences were 3.2 ms (−9.4 to 15.7 ms, p=0.61), 1.2 ms (−9.7 to 12.0 ms, p=0.82), and −0.3 ms (−8.0 to 7.4 ms, p=0.94) for rMSSD, SDNN, and HRV triangular index, respectively. The distribution of the HRV variables is presented in Figure 1.

The two groups had no statistically significant differences in the secondary objectives of minimum, mean, and maximum HR or QTc interval over 24 hours (Table 3). Although the PI regimen group exhibited numerically lower HR values (minimum: −1.4 bpm [−8.1 to 5.2 bpm, p=0.67], mean: −4.3 bpm [−10.1 to 1.6 bpm, p=0.15], maximum: −7.2 bpm [−18.6 to 4.2 bpm, p=0.21]) (Figure 2) and numerically longer QTc intervals (minimum: 7.0 ms [−15.7 to 29.6 ms, p=0.53], mean: 10.3 ms [−7.2 to 27.7 ms, p=0.24], maximum: 2.9 ms [−21.4 to 27.1, p=0.81]) (Figure 3) than the control group, the differences were not statistically significant.

Discussion

The present study investigated whether PIs elevate parasympathetic activity, as measured by subclinical markers like HRV. Early detection of such effects in risk populations could help prevent clinically significant bradycardia or conduction defects. To isolate the impact of PIs, the authors excluded participants taking other medications, those with active infections, and those with existing comorbidities. While daily activities and age were not controlled, these factors were considered potential confounders. The key findings of our study were as follows: 1) The use of a PI

Table 2. Demographic and baseline characteristics of participants

	All participants (n=30)	PI regimen (n=12)	Non-PI regimen (n=18)	p-value*
Age	44.6±9.0	46.6±10.0	43.2±8.3	0.33
Male, n (%)	20 (66.6)	8 (66.6)	12 (66.6)	-
Height (cm)	165.7±8.8	165.8±8.5	166.9±9.0	0.36
Weight (kg)	64.9±13.7	58.9±8.7	68.8±15.1	0.05
BMI (kg/m^2)	23.6±4.7	22.0±3.0	24.6±5.4	0.13
CD4 level (cells/ml^3)	665.6±229.0	606.6±155.6	705.0±263.9	0.26
Heart rate (bpm)	65.6±8.7	64.0±8.6	66.7±8.9	0.42
PR interval (ms)	160.6±21.2	162.3±20.2	159.5±22.3	0.73
QRS duration (ms)	99.0±14.6	105.3±17.6	94.8±10.8	0.05
QTc interval (ms)	407.7±23.4	409.0±27.2	406.8±21.2	0.80
Hemoglobin (g/dL)	15.4±5.4	14.1±1.1	16.2±6.8	0.28
Creatinine (mg/dl)	1.0±0.2	1.1±0.3	0.9±0.2	0.07

The p-values were derived from the unpaired t-test. All variables were presented as means ± SD or number (percentage)

BMI=body mass index; bpm=beats/min; PI=protease inhibitor; ms=millisecond

Table 3. 24-hour Holter monitoring analysis

	PI regimen (n=12)	Non-PI regimen (n=18)	Mean difference	p-value*
rMSSD (ms)	29.0±15.8	25.8±16.8	3.2 (-9.4 to 15.7)	0.61
SDNN (ms)	47.9±10.3	46.7±16.2	1.2 (-9.7 to 12.0)	0.82
HRV triangular index	33.5±9.2	33.8±10.7	-0.3 (-8.0 to 7.4)	0.94
minimum HR (bpm)	49.8±8.8	51.2±8.7	-1.4 (-8.1 to 5.2)	0.67
mean HR (bpm)	75.1±6.8	79.3±8.2	-4.3 (-10.1 to 1.6)	0.15
maximum HR (bpm)	119.7±14.7	126.8±15.1	-7.2 (-18.6 to 4.2)	0.21
minimum QTc interval (ms)	393.9±29.1	386.9±30.0	7.0 (-15.7 to 29.6)	0.53
mean QTc interval (ms)	432.8±22.4	422.6±23.1	10.3 (-7.2 to 27.7)	0.24
maximum QTc interval (ms)	498.3±41.8	495.4±23.0	2.9 (-21.4 to 27.1)	0.81

P-values were derived from the unpaired t-test. All variables were presented as means ± SD.

bpm=beats/min; PI=protease inhibitor; ms=millisecond; rMSSD=square root of the mean of the sum of the squares of differences between adjacent NN intervals SDNN=standard deviation of all NN intervals.

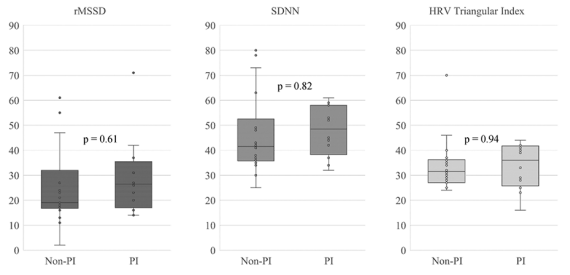

Figure 1. Heart rate variability variables distribution.

HRV=heart rate variability; PI=protease inhibitor; rMSSD=root mean square of the successive differences between normal RR intervals; SDNN=standard deviations of all NN intervals; body mass index.

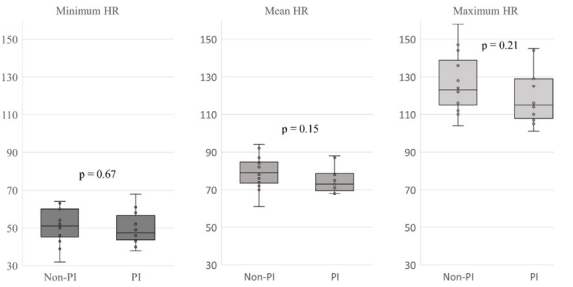

Figure 2. 24-hour heart rate variables distribution.

HR=heart rate; PI=protease inhibitor

regimen was associated with a slower heart rate compared to the non-PI regimen. However, there were no significant differences. 2) There were no significant differences in HRV time domain analysis or QTc intervals between the PI and non-PI groups.

The results of our study align with previous cross-sectional study findings regarding lower heart rates in patients on a PI regimen[21]. However, the limited sample size in our study led to insufficient statistical power to demonstrate significant differences, as reported in previous studies. Although the observed differences did not reach statistical significance, patients receiving the PI regimen tended to have lower heart rates (HRs) and longer QTc

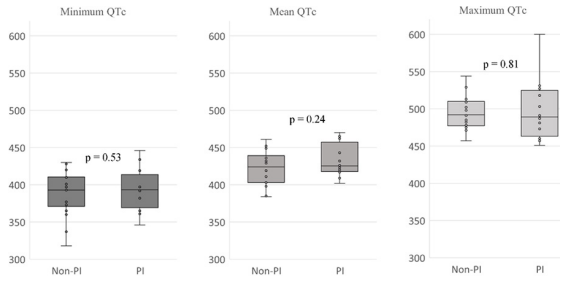

Figure 3. 24-hour QTc variables distribution.
PI=protease inhibitor; QTc=corrected QT interval

intervals than those in the non-PI group. Regarding HRV, the method of investigation differs between studies. The SMART study utilized ECG to analyze HRV[21]. Our study employed 24-hour Holter monitoring, allowing longer HRV monitoring than ECG. Interpreting the measure of autonomic function may be challenging due to its dynamic nature throughout the day. The authors hypothesize that extending the monitoring period will increase sensitivity for detecting autonomic dysregulation. However, extending the analysis duration, the HRV analysis results are similar for both PI and non-PI regimens, comparable to the findings of a former study. The findings from the previous study indicate cardiac autonomic dysfunction characterized by reduced cardiac vagal modulation in HIV-infected patients compared to non-HIV infection. In contrast, the HIV-infected patients were similar in both PI and non-PI regimens[23]. Our baseline patients' mean CD4 levels are quite high, exceeding 500 cells/mm^3 (mean CD4 level in our study = 665.6 cells/mm^3), consistent with previous studies' findings. This may be explained by the fact that patients in our cohort are generally healthy with well-controlled viral loads and high CD4 levels. However, some previous studies have shown that autonomic dysfunction is not related to the duration of HIV, HIV-RNA levels, CD4 cell count, CD4 nadir, ART duration, or the use of protease inhibitors (PIs)[24]. Autonomic dysfunction in HIV-infected patients is more pronounced in those with acquired immunodeficiency syndrome (AIDS) compared to those without AIDS (16% vs. 4%)[25].

Studies comparing different classes of ART have shown that patients receiving protease inhibitors (PIs) tend to have preserved cardiac autonomic function. In contrast, other studies suggest a deleterious association between ART and an increased risk of myocardial infarction or heart failure[26]. The proposed mechanism behind NNRTI and non-boosted PI regimens affecting heart rate variability could stem from their detrimental atherogenic impacts[27]. This possibility is partially supported by the observed differences in lipid profiles among various ART regimens[28]. Additionally, several ART drugs have been linked to the development of toxic neuropathy[29,30]. Therefore, another possibility is that disparities in neurotoxicity could lead to variations in the associations between ART drugs and markers of cardiac autonomic function.

Limitations

The present study had some limitations. First, the sample size was relatively small. This may have limited our ability to detect statistically significant differences between the groups. Second, the data was collected using Holter monitors over 24 hours. While we implemented strict exclusion criteria to minimize the influence of confounding factors, unidentified confounders may still have affected our results. Variations in daily activities or obstructive sleep apnea could introduce noise or bias into the data. A limitation of the cross-sectional study design is the potential for day-to-day fluctuations in patient data, which may lead to a lack of statistical significance in this analysis and preclude temporal evaluation of the treatment effects on cardiac autonomic parameters. These weaknesses could be addressed by extending ECG monitoring or collecting data at multiple time points. However, the authors designed our study with practical applications in mind. Finally, the Holter analysis program is limited to analyzing specific time segments and only provides linear measurements in the time and frequency domains. It does not support non-linear HRV analysis. Future research could explore the benefits of time-specific analyses using Holter monitoring, such as nighttime measurements only. Confounding effects could also be further reduced by excluding participants with sleep apnea and requesting abstinence from activity, significantly increasing HR during the monitoring period.

Conclusion

Using 24-hour Holter monitoring analysis, the present study did not identify any statistically significant differences in autonomic function, as measured by HRV, or in the QT intervals between participants with HIV receiving PI regimens and those receiving non-PI regimens.

What is already known on this topic?

Reduced heart rate variability (HRV), indicating cardiac autonomic dysfunction, has been documented in individuals with HIV infection.

The influence of protease inhibitors (PIs) on cardiac autonomic functions remains uncertain due to their positive impact on suppressing HIV, alongside their negative effects on promoting diabetes and atherosclerosis.

24-hour Holter monitoring is a means of HRV assessment that can be used to identify dysfunction within the cardiac autonomic nervous system. However, the effectiveness of this technique in detecting early-stage autonomic dysregulation in HIV patients receiving PI

therapy remains unclear.

What this study adds?

There is no difference in HRV between patients receiving PI treatment and those not receiving PI treatment.

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Conflicts of interest

The authors declare no conflict of interest.

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