Journal of Electrocardiology 55 (2019) 133–137

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

R-peak time: A novel marker of depolarization in patients with Human Immunodeficiency Virus☆

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ARTICLE INFO

Introduction

In recent years, there has been renewed interest in cardiovascular mortality in Human Immunodeficiency Virus (HIV)-infected population. In addition to acquired immune deficiency syndrome (AIDS) [1], cardiovascular abnormalities including cardiomyopathy [2], pulmonary hypertension [3], and prolonged corrected QT interval [4] were strongly associated with mortality in HIV-infected patients. Moreover, it has been shown that the risk for sudden cardiac death (SCD) among HIV-infected population elevated 4.5-fold compared with predicted rates in the general population [5]. Increased prevalence of cardiovascular disease (CVD) in this population, SCD is likely an essential contributor to overall mortality.

A transgenic murine model of HIV infection has shown obtained sodium and potassium channelopathy, observing this may directly influence cardiovascular depolarization and repolarization, in this way leading HIV-infected patients to ventricular arrhythmias [6,7].

R-peak time (ventricular activation time) mainly reflects the time of transmural impulse propagation from endocardium to epicardium as gathered by the recording electrode depending on the lead type: a unipolar precordial lead, a bipolar or unipolar limb lead. Previously, the malignant arrhythmic risk indices including the prolongation of the QRS complex and the QT which were observed in HIV. However, there has been no detailed investigation of R-peak time, a ventricular activation indicator, in the HIV-infected patients [8,9].

This study aimed to evaluate R-peak time in adults infected with HIV, compared to the normal healthy population.

Methods

In this single-center, retrospective study, we conducted a comprehensive search from January 1, 2016, to December 31, 2018, for the patients who admitted for infections in which HIV was identified. The following data were gathered from the patient records: age, gender clinical presentation, electrocardiographic and echocardiographic imaging.

Power analyses of the study were performed using the program of G*Power (Version 3.1.9.2) power-and-sample size calculation (Düsseldorf Universität, Germany). The sample size was estimated based on the probable number of participants that could be identified in a reasonable time with a 2:1 allocation ratio. A calculation of sample size revealed that at least 198 patients for all groups were needed to detect differences between results with a statistical power (1-β value) of 95% allowing for a type (α) error of 0.05. Of those 198 patients, 66 should be placed in the HIV-infected group, and 132 should be placed in the control group with actual power. A total of 210 participants were selected in the current study. The HIV group consisted of 70 subjects (40 men, with a median of 38 (30 to 47) years), and the control group included of 140 individuals (95 men, with a median of 36 (27 to 56) years).

Patients with valvular heart disease, other congenital heart diseases, documented coronary artery disease, pulmonary hypertension, chronic renal/kidney failure, chronic lung disease, pregnancy, malignancy, electrolyte imbalance, paced rhythms, bundle branch block, atrioventricular conduction abnormalities were excluded from the study. The first CD4+ lymphocyte counts were assessed in the patients' medical documents. None were taking any antiarrhythmic drugs and antiretroviral drugs that could affect the electrocardiographic measurements at the time of admission. Informed consent was obtained from the control group involved in this study. The study was approved by the Institutional Ethics Committee.

Blood samples were drawn via the antecubital vein at admission (following a fasting period of 12 h) and collected in Becton Dickinson Vacutainer tubes containing 3.6 mg of K2EDTA (dipotassium ethylenediaminetetraacetic acid) for hematological tests and in yellow biochemistry tubes without anticoagulant for biochemical tests. Glucose, creatinine, and lipid profile were determined by standard methods [10]. An automatic blood counter (Sysmex XT 2000i Hematology Analyzer; Sysmex, Kobe, Japan) was used for whole blood counts.

Echocardiography was performed with an echocardiography platform (GE Vivid 3, GE Healthcare, Piscataway, New Jersey, USA) equipped with a 1.5–3.6 MHz phased-array probe in the left lateral decubitus position. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule [11].

☆ There is no funding for this research to declare.There is no conflict of interest.
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https://doi.org/10.1016/j.jelectrocard.2019.05.016

ECGs were recorded digitally at 10 mm/mV calibration at a speed of 25 mm/s for 10 s in the supine

position. QT interval (from the onset of the QRS complex to the end of the T wave) and corrected QT interval (according to the Bazett's formula (QTc = QT/RR)) were measured [12].

Definitions

Advanced HIV disease was defined as WHO stage 3 or 4 and CD4 cell count <200/mm^3 [13]. R-peak time has established the interval from the earliest onset of the QRS complex to the peak of the R wave or R′ if present. Irrespective of the relative height of the R and R′ waves, the R-peak time was measured to the second peak in both the limb (unipolar and bipolar) and precordial leads [14,15]. The R-peak time's upper limit of normal is 35 ms for the thinner-walled right ventricle (measured from lead V1 or V2) and 45 ms for the left ventricle (LV) (measured from leads V5 to V6) [16]. Measurements of the R-peak time were performed in all 12 leads. For the left ventricle, R-peak time-mean was (R-peak time of each of the leads was summed and divided by 12) taken as the mean value of 12 leads, R-peak time-anterior was taken as the mean value of anterior leads (V1, V2, V3, V4, V5, V6), R-peak time-lateral was taken as the mean value of lateral leads (D1, aVL, V5, V6), R-peak time-inferior was taken as the mean value of inferior leads (DII, DIII, aVF) and for the right ventricle (RV), R-peak time-RV was taken as the mean value of V1 and V2. The intraobserver and interobserver variability of the R-peak time measurements was assessed using 20 randomly selected ECGs measured by two independent cardiologists. Investigators were blinded as to the clinical status of the subjects. Intraobserver and interobserver coefficients of variation (standard deviation [SD] of differences between two observations divided by the mean value and expressed as the percent) were 2.3% and 2.7%, respectively.

Statistics

Statistical analyses were performed using SPSS software version 22 (SPSS Inc. Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Continuous variables were presented as a mean ± SD or medians (interquartile ranges), whereas categorical variables were summarized as the number of cases with the percentage (%). Overall comparisons of categorical variables were performed using Pearson's χ^2 test and Fisher's exact test. Student *t*-test was used for normally distributed parameters, whereas Mann Whitney *U* test was used for the parameters not distributed normally. Pearson correlation analysis was performed to examine the relationship between mean R-Peak time and other variations. A p value < 0.05 was accepted as statistically significant.

Results

The baseline clinical data and laboratory parameters are presented in Table 1. The study population was divided into two groups which were similar regarding sex distribution, age, body mass index, smoking status and basal laboratory findings ($p > 0.05$). Electrocardiographic parameters of the groups are shown in Table 2. The QRS, RR and QT interval were similar between the groups ($p = 0.216$, $p = 0.412$, $p = 0.079$, respectively). QTc interval was significantly increased in HIV patients compared to the controls ($p = 0.006$). R-peak time-V4, R-peak time-V5, R-peak time-V6, R-peak time-mean, R-peak time-anterior and R-peak time-lateral were also significantly high in HIV patients compared to the control group ($p = 0.021$, $p = 0.007$, $p = 0.033$, $p = 0.035$, $p = 0.017$, $p = 0.043$, respectively). There were no significant differences between the two groups regarding their EF ($p = 0.876$). In correlation analysis, there was inverse correlation between mean R-peak time and CD4 count ($r = -0.326$, $p = 0.015$). In detailed analysis, anterior wall R-peak time and CD4 count showed inverse correlations ($r = -0.333$, $p = 0.013$). Besides, there was correlation between R-peak interval with hsCRP ($r = 0.278$, $p = 0.041$) (Fig. 1).

Table 1
Clinical characteristics and laboratory findings of the study population.

Variables	HIV patients (n = 70)	Control group (n = 140)	p value
Age (years)	38 (30–47)	36 (27–56)	0.712
Men, n (%)	40 (57%)	95(68%)	0.117
Smoking (%)	29.1%	35.5%	0.353
BMI	23.6 ± 3.3	22.8 ± 4.5	0.188
Hemoglobin, g/dl	13.8 ± 2.1	12.9 ± 4.3	0.099
Glucose, mg/dl	95.1 ± 7.4	94.3 ± 8.3	0.496
Urea, mg/dl	13.4 ± 4.3	13.7 ± 1.6	0.465
Serum creatinine, mg/dl	0.9 ± 0.2	0.8 ± 0.5	0.109
Total cholesterol, mg/dl	178.2 ± 47.2	169.9 ± 51.5	0.259
LDL cholesterol, mg/dl	113.0 ± 33.7	121.7 ± 43.6	0.144
HDL cholesterol, mg/dl	41.0 ± 14	43.4 ± 9	0.134
Triglycerides, mg/dl	153.8 ± 75.1	149.7 ± 52.2	0.644
hs-CRP, mg/dl	3 (1–5)	–	–
CD4 count, (cells/mm^3)	360 (152–576)	–	–

Data are given as median (IQR), mean ± SD, or n (%). HDL, high-density lipoprotein; HIV, Human Immunodeficiency Virus; LDL, low-density lipoprotein.

Discussion

The most obvious finding emerges from the analysis is that R-peak time was prolonged in HIV patients as compared to healthy subjects. R-peak time which reflects the time elapsed for the depolarization to spread from the endocardium to epicardium is being used in various clinical conditions to facilitate diagnosis and in some circumstances, to determine prognosis [17,18]. Prolongation of R-peak time indicates reduced cardiac excitability, which could lead to the generation of cardiac arrhythmias. Thus, as the present study shows, the extension of the R-peak time in HIV may be attributable to a HIV-mediated reduction in ventricular Na+ current leading impaired action potential propagation, conduction block, and reentrant arrhythmias [19]. Indeed, the previous report showed that ventricular Na+ currents are decreased in HIV-infected mice [20].

Furthermore, we found that the prolonged R-peak time showed a negative correlation with CD4 count. A possible explanation of this might be ventricular activation time significantly increases in parallel

Table 2
Electrocardiographic and echocardiographic characteristics of the study population.

Variables	HIV patients (n = 70)	Control group (n = 140)	p value
Heart rate (bpm)	73.2 ± 10.6	71.6 ± 12.2	0.351
RR interval (ms)	840.1 ± 145.0	860.4 ± 179.4	0.412
QRS interval (ms)	91.4 ± 10.7	95.0 ± 16.9	0.216
QT interval (ms)	367.4 ± 36.4	381.4 ± 58.5	0.079
QTc interval (ms)	400.3 ± 29.2	415.5 ± 62.2	0.006
R-peak time-DI	31.3 ± 6.7	29.3 ± 6.6	0.351
R-peak time-DII	32.9 ± 8.7	32.3 ± 10.0	0.749
R-peak time-DIII	31.8 ± 9.3	28.4 ± 10.6	0.051
R-peak time-aVR	30.8 ± 7.5	28.5 ± 5.1	0.112
R-peak time-aVL	29.8 ± 9.0	26.7 ± 6.6	0.143
R-peak time-aVF	31.4 ± 9.0	29.3 ± 10.2	0.160
R-peak time-VI	30.4 ± 9.0	27.7 ± 6.2	0.108
R-peak time-V2	28.9 ± 8.9	27.3 ± 5.2	0.289
R-peak time-V3	31.8 ± 7.6	29.3 ± 6.1	0.254
R-peak time-V4	31.6 ± 8.4	28.5 ± 6.4	0.021
R-peak time-V5	32.8 ± 7.4	28.6 ± 6.1	0.007
R-peak time-V6	32.8 ± 8.7	28.9 ± 6.0	0.033
R-peak time-mean	31.3 ± 6.3	28.2 ± 3.3	0.035
R-peak time-anterior	31.7 ± 6.5	27.9 ± 3.7	0.017
R-peak time-lateral	31.7 ± 6.6	28.3 ± 4.4	0.043
R-peak time-inferior	32.1 ± 8.3	30.0 ± 8.9	0.290
R-peak time-RV	29.7 ± 8.3	27.5 ± 5.1	0.141
LVEF, (%)	64.1 ± 5.4	65.1 ± 3.5	0.107

Data are given as mean ± SD or %. LVEF, left ventricular ejection fraction; RV, right ventricle.

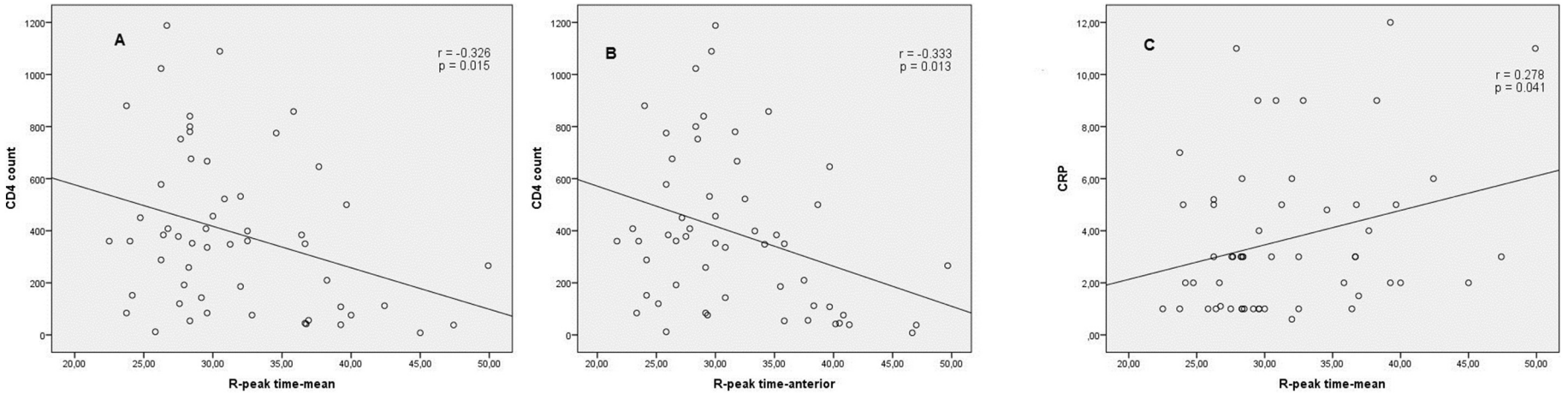

Fig. 1. (A) Correlation between R-peak time-mean and CD4 count. (B) Correlation between R-peak time-anterior and CD4 count. (C) Correlation between R-peak time-mean and hs-CRP.

to the severity of the disease. In our study, even though HIV-infected patients did not express overt cardiomyopathy and heart failure, anterior wall R-peak time prolongation was apparent. This may attribute the subclinical cardiac mechanical dysfunction and the presence of myocardial abnormalities (fibrosis and steatosis). Overall, this evidence suggests that prolongation R-peak time observed in the HIV-infected patients may be secondary to HIV induced cardiac remodeling.

C-reactive protein (CRP) is a well-known acute phase protein that is delivered predominantly by hepatocytes in light of several cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNFα) [21]. Previously, several studies have shown that proinflammatory cytokines TNFα and IL-1β increased in HIV patients [22,23]. In a comprehensive survey of Grandy et al. reported the link between elevated serum proinflammatory cytokines and the reduction of the action potential (AP) amplitude in ventricular myocytes from a mouse model [20]. As the evidence shows the importance of the level of inflammation, it is convincing to suggest significant positive correlations between the inflammatory marker hs-CRP and R-peak time in our study. These results may be explained by the fact that high proinflammatory cytokines could alter Na+ channel function, thus changing cardiac depolarization and lead to the generation of arrhythmias.

Corrected QT interval and QT dispersion, known as traditional ventricular repolarization markers, have been utilized in numerous illnesses described by malignant ventricular arrhythmias, for example, myocardial infarction, coronary artery disease, hypertrophic cardiomyopathy, chronic heart failure and long-QT syndrome [24–26]. Besides, previous studies have revealed a relationship between HIV infection and prolongation of the QT interval which aggregate malignant ventricular arrhythmias [9,27,28]. Some antiretroviral agents, including protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), antiretroviral therapy (ART) and cytochrome-P450-dependent drugs' interactions, opioid usage and HIV virus effects on cardiac ion hERG K+ channels that alter QT intervals have been described as the main causes of the QT prolongation [29]. Consistent with the literature, we found that QTc interval was significantly higher in HIV patients when compared to controls. Furthermore, this occurred in the absence of any pharmacological intervention. These results reflect those of J. Brouillette et al.'s who reported prolonged QTc in HIV patients was independent of drug therapy. They identified the mechanism that underlies HIV-related alterations in ventricular repolarization was an attributable reduction in outward K+ currents [6].

The findings of our study should be interpreted with caution because of the limited sample size and retrospective origin. We investigated the electrocardiographic features of HIV-infected patients, before starting antiretroviral drug treatment. The subsequent follow-up of these patients on antiretroviral drug treatment was not addressed. Also, due to the cross-sectional nature of the study, the patients were not followed for the future arrhythmic events that may have the relation between ventricular arrhythmias and the R-peak interval. Additionally, we did not evaluate proinflammatory cytokines TNFα and IL-1. Therefore, prospective randomized studies in a larger population are required to confirm our results.

Conclusion

The key strength of the present study is to show prolongation of R-peak time in HIV-infected patients. Furthermore, this appears to be the first study to suggest that R-peak time could play a role in developing new risk stratification scores focusing on HIV-infected individuals. And the present study lays the groundwork for future search into the markers of HIV related arrhythmia and the mortality.

Author contribution

All authors contributed to the conception of the work and drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of competing interests

The authors declared no potential conflicts of interest concerning the research, authorship, and publication of this article.

Funding

The authors received no financial support for the research, authorship, and publication of this article.

Acknowledgments

We thank Engin Ates for assistance with "ECG Tool" that greatly provided the ECG measurements and improved the manuscript.

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