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Cardiac arrhythmias, conduction system abnormalities, and autonomic tone in patients with brucellosis

S. GÜNLÜ[1], A. AKTAN[2]

[1]Department of Cardiology, Dağkapi State Hospital, Diyarbakir, Turkey
[2]Department of Cardiology, Mardin Training and Research Hospital, Mardin, Turkey

Abstract. – OBJECTIVE: Arrhythmias can occur because of cardiac involvement in patients with brucellosis. We investigated the effect of Brucella *(Brucella melitensis)* on cardiac arrhythmias in patients without pre-existing arrhythmogenic heart disease.

PATIENTS AND METHODS: 205 patients with sinus rhythm who were diagnosed with brucellosis and 205 healthy controls were enrolled. ECG was performed, and the parameters were recorded for each patient. 24-hour ambulatory ECG (Holter) monitoring was conducted, and the recordings were analyzed. The time-domain heart rate variability (HRV) results were evaluated.

RESULTS: The average age of the group with brucellosis was 28.9±6.4 years, and 57.1% were male. The ECG parameters, including P dispersion (Pd), QT dispersion (QTd), corrected QTd (QTcd), T-peak to T-end (TpTe), and corrected TpTe (TpTec) were longer and TpTe/QT, TpTe/QTc, TpTec/QT, and TpTec/QTc ratios were higher in the study group compared to the control group ($p<0.05$). Holter monitoring recorded 33 (16.1%) patients in the study group and 3 (3%) in the control group with abnormal rhythms. In the brucellosis group, low frequency (LF), low/high frequency (LF/HF), and the standard deviation of all R-R intervals (SDNN) values, which are known HRV indicators, were substantially different than in the control group ($p<0.001$).

CONCLUSIONS: We can evaluate the silent involvement of the cardiac conduction system in patients with brucellosis using ECG parameters, which is a non-invasive and simple method in terms of feasibility in clinical follow-up.

Key Words:
Brucellosis, Holter monitoring, Arrhythmia, QRS-T angle, Heart rate variability.

Introduction

Brucellosis, a zoonotic infectious disease, is increasing worldwide[1]. Despite the diagnosis and increasing number of reports, the true prevalence remains unknown[2,3]. As a systemic infection, it can affect all organs and cause various clinical signs and symptoms. It mostly affects the musculoskeletal, gastrointestinal, blood, urogenital, and skin systems[4].

Although cardiac involvement is less than 2% in patients with brucellosis, it can increase to 7%/10% in endemic regions. Catastrophic consequences such as endocarditis and heart failure can be observed in untreated patients[5]. Myocardial injury can lead to the occurrence of malignant arrhythmias by affecting the cardiac conduction system[6,7]. ECG parameters, including P dispersion (Pd), QT dispersion (QTd), corrected QTd (QTcd), T-peak to T-end (TpTe), and corrected TpTe (TpTec), TpTe/QT, TpTec/QT, TpTe/QTc, TpTec/QTc, and frontal QRS-T angle can help to predict atrial and ventricular arrhythmias[8]. Heart rate variability (HRV) indicators may play a role in estimating the correlation between brucellosis and autonomic nervous system dysfunctions. Holter monitoring is commonly used as a non-invasive method for detecting arrhythmia which is not found in ECG. Holter monitoring can also evaluate HRV by measuring short-term (beat-to-beat) heart rate fluctuations.

In this study, we aimed to estimate the subclinical cardiac conduction system involvement of *Brucella* infection using ECG parameters and to evaluate HRV parameters in predicting autonomic nervous system dysfunction using Holter.

Patients and Methods

Study Design and Subjects

The study was conducted between 2017 and 2021. The study population was established through a cross-sectional evaluation of patients diagnosed with brucellosis. 268 patients aged 18-75 years, who had sinus rhythm and whose Holter monitoring was performed after diagnosis, were included. Data were obtained from the hospital

Corresponding Author: Nerhat Günlü, MD; e-mail: serhat8086@hotmail.com

records. 63 patients were excluded based on the exclusion criteria listed below. 205 patients were included in the control group.

The exclusion criteria were as follows: hypertension, congenital cardiac disease, dysrhythmia, ischemic heart disease, cardiomyopathies, chronic obstructive pulmonary disease, asthma, electrolyte disorder chronic renal disease, obesity, anxiety, diabetes mellitus, vitamin deficiency, and any infectious disease other than brucellosis.

The patients were administered doxycycline 100 mg PO twice daily for 6 weeks and streptomycin 1 g/day IM regimen for 2-3 weeks according to the World Health Organization (WHO) guideline recommendations.

Study Protocol

A 12-lead ECG was performed with an electrocardiograph (model ECG-1350K Nihon-Kohden Corporation, Tokyo, Japan) at a rate of 25 mm/s and 10 mm/mV amplitude. A scanner was used to computerize the existing ECGs. Two separate cardiologists calculated and analyzed the TpTe time under x400 percent magnification. A significant and almost perfect agreement was found between the cardiologists (κ=0.861). The Bazett formula was used to correct the TpTe and QT intervals for heart rate. ECG analysis automatically measured the QT interval, QTc interval, QRS, and T axis, therefore these data were collected directly. Utilizing the difference between the QRS and T axis, the frontal QRS-T angle was computed.

The P dispersion was calculated by minus the smallest P wave duration from the highest P wave duration[9]. Similarly, QT and QTc dispersion was calculated.

Standard 24-hour, three-leads (leads V1, V2, and V5) Holter ECG (Northeast Monitoring, Maynard, MA, USA) recordings were used to evaluate the patients. After manually adjusting R-R intervals, the records were analyzed utilizing a Century 2000/3000 HRV system (Biomedical Systems, Maryland Heights, MO, USA). Throughout the recordings, the patients remained in a supine position and had fasted overnight. Intervals between normal and ectopic beats and between ectopic beats, as well as intervals assessed incorrectly due to artifacts, were eliminated from the analysis. The time-domain analysis examined the mean heart rate, the root mean square of successive differences (RMSSD), the standard deviation of R-R intervals (SDNN), and the number of R-R intervals deviating by more than 50 ms from adjacent intervals divided by the total number of R-R intervals (pNN50). Applying the fast Fourier transform method, spectral measurements were obtained. Recordings were averaged over five different 5-minute sessions, according to the Heart Rhythm Societ[10]. The total power was categorized as high frequency (HF) and low frequency (LF) components.

Statistical Analysis

All analyses were performed with the SPSS program version 24.0 (Statistical Package for Social Science, IBM Corp., Armonk, NY, USA). The initial continuous variables were expressed as mean±standard deviation or median (interquartile range) according to the given data. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages. Nominal variables were compared using the chi-squared test or Fisher's exact test. The statistical significance was defined as *p*-values <0.05.

Results

The average age of the group with brucellosis was 28.9±6.4 years, and 57.1% were male. The mean age of the control group was 28.1±5.3 years. White blood cells (Wbc), aspartate aminotransferase (Ast), C-reactive protein (Crp), and erythrocyte sedimentation rate (Esr) were substantially higher in the study group (p<0.001), whereas hemoglobin (Hg), hematocrit (Hct), and platelets (Plt) were higher in the control group (p<0.001). Alanine aminotransferase (ALT), creatinine, urea, sodium, potassium, and low-density Lipoprotein Cholesterol (LDL-C) levels were not significantly different between groups (p>0.05). There was no significant difference between groups in terms of ejection fraction (p=0.291) (Table I). In Holter monitoring of brucellosis patients, abnormal ECG findings were found in 33 (16.1%) patients, while abnormal ECG findings were found in only 3 (3%) patients in the control group. The distribution of abnormal rhythms in the brucellosis group is depicted in Figure 1. In the brucellosis group, SDNN was lower, and LF and LF/HF were significantly higher than in the control group (p<0.001). However, there were no significant differences in RMSSD (p=0.178), pNN50 (p=0.096), or HF (p=0.058) (Table II). A comparison of ECG parameters between the groups is shown in Table III. There were substantial disparities between groups in terms of ECG parameters.

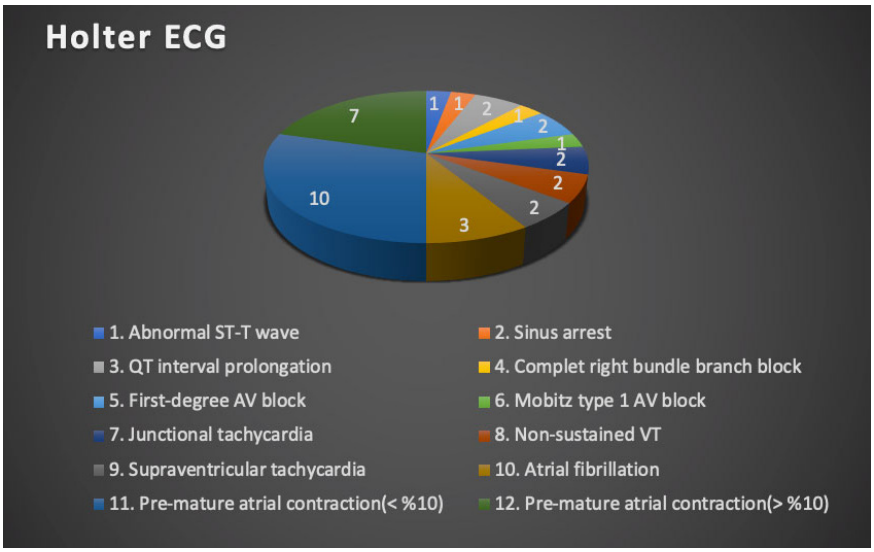

Figure 1. Number of abnormal rhythms detected in Holter recordings of the study group.

Table I. Demographic and laboratory findings of groups.

	Study group (n=205)	Control group (n=205)	*p*-value
Age (Years)	28.9±6.4	28.1±5.3	0.190
Sex, male, n (%)	117 (57.1%)	132 (64.4%)	0.129
WBC (K/mm^3)	9.5±2.7	8.1±1.6	<0.001
HGB (g/dl)	13.7±1.7	15.0±1.1	<0.001
HCT (%)	40.9±5.0	45.0±3.5	<0.001
PLT (K/mm^3)	246.1±64.0	277.3±36.4	<0.001
AST (U/L)	19.6±6.9	16.2±6.4	<0.001
ALT (U/L)	16 (12-23)	16 (12-25)	0.613
CRP (mg/L)	0.6 (0.32-1.4)	0.2 (0.1-0.3)	<0.001
Creatinine, mmol/L	0.76±0.14	0.74±0.14	0.121
Urea, mmol/L	28.2±10.2	27.6±10.0	0.528
Sodium, mEq/L	139.3±3.1	139.7±3.1	0.256
Potassium, mEq/L	4.1±0.4	4.0±0.4	0.112
LDL-C mmol/L	90.3±23.0	89.4±24.5	0.716
ESR (mm/hr)	18 (14-24)	14 (11-16)	<0.001
EF %	56.7±4.8	57.2±4.6	0.291

Data are expressed as mean ± SD and median [interquartile range] as appropriate. WBC: White blood cells, HGB: Hemoglobin, HCT: Hematocrit, PLT: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, LDL-C: Low-density lipoprotein cholesterol, ESR: erythrocyte sedimentation rate, EF: Ejection fraction.

Table II. Heart rate variability parameters of groups.

	Study group (n=205)	Control group (n=205)	*p*-value
SDNN (ms)	103.4±46.7	138.4±19.7	<0.001
RMSSD (ms)	30.6±13.5	28.8±13.7	0.178
pNN50 (%)	9.7±3.7	9.0±4.1	0.096
LF (nu)	69.8±15.3	58.0±16.2	<0.001
HF (nu)	30.5±5.3	29.4±5.5	0.058
LF/HF	2.37±0.72	2.05±0.76	<0.001

Data are expressed as mean ± SD and median [interquartile range] as appropriate. SDNN: Standard deviation of the NN (R-R) intervals, RMSSD: Root mean square of the successive differences, pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals, LF: Low frequency, HF: High frequency.

Table III. Comparison of ECG parameters between groups.

	Study group (n=205)	Control group (n=205)	*p*-value
Pmax (ms)	119.7±8.1	112.3±6.0	<0.001
Pmin (ms)	72.4±9.1	81.7±8.5	<0.001
Pd (ms)	47.3±12.7	30.6±6.3	<0.001
QTd (ms)	51.2±7.9	38.7±7.0	<0.001
QTcd (ms)	68.2±8.2	54.9±6.7	<0.001
TpTe (ms)	73.4±10.1	69.3±8.9	<0.001
TpTec (ms)	78.6±11.2	75.7±12.6	0.014
TpTe/QT	1.86±0.30	1.45±0.41	<0.001
TpTe/QTc	1.28±0.21	1.09±0.22	<0.001
TpTec/QT	2.02±0.34	1.57±0.51	<0.001
TpTec/QTc	1.40±0.21	1.16±0.29	<0.001
Heart rate (beats/min)	74.9±9.6	73.8±9.5	0.228
Frontal QRS-T angle	49.9±7.6	38.6±6.9	<0.001
Abnormal ECG rhythm, n (%)	32 (15.6)	13 (6.3)	0.003

Data are expressed as mean ± SD and median [interquartile range] as appropriate. Pmax: P maximum, Pmin: P minimum, Pd: P dispersion, QTd: QT dispersion, QTcd: QTc dispersion, TpTe: T-peak to T-end, TpTec: Corrected TpTe.

Discussion

This study showed that the durations of Pd, QTd, QTcd, TpTe, and TpTec were longer and TpTe/QT, TpTe/QTc, TpTec/QT, and TpTec/QTc ratios were higher in the study group compared to the controls. Additionally, patients with brucellosis had significant dysfunction of the autonomic nervous system in favor of the sympathetic system when compared to the control group.

Cardiac involvement in *Brucella* infection can manifest in various forms, including endocarditis, myocarditis, and pericarditis; however, endocarditis is the most prevalent complication[11]. Myocardial involvement may occur directly by microorganisms or indirectly through the accumulation of immune complexes[12]. In the case of inflammation, fibroblast activation, collagen deposition, and immunocyte infiltration cause myocardial damage and affect the cardiac conduction system[13]. Occasionally, the cardiac conduction system may be affected by pro-inflammatory mediators without myocardial damage[14,15]. Pathological changes may cause atrial or ventricular arrhythmias[16]. If malignant arrhythmia develops, it can result in death[17,18]. The development of arrhythmia can be predicted by using non-invasive methods.

Paroxysmal atrial fibrillation (PAF) can be predicted independently by Pd. It has been reported[19-21] that inflammation prolongs the Pd duration in patients with RA, Psoriasis, and Behçet's, thus increasing the risk of atrial fibrillation.

Studies[22,23] have shown that with prolonged QTd, ventricular arrhythmias are triggered, and sudden cardiovascular death develops. Vasyuk et al[24] reported that ventricular arrhythmias due to long QTd were more common in patients with acute brucellosis and ventricular tachycardia was observed in 7 of 110 patients with acute brucellosis. Sayar et al[25] observed that a patient who developed torsades de pointes (TdP) due to *Brucella* endocarditis stabilized after medical treatment and the QT interval became normal. In addition, trimethoprim-sulfamethoxazole, which is used in the treatment of *Brucella* and increases the QT interval, was not given to the patients because it increased the risk of torsades de pointes. In our study, it was not given to the patients, too. This result highlights the importance of early diagnosis and appropriate treatment in patients with cardiac involvement.

Several ventricular repolarization metrics, including TpTe time, TpTe/QT ratio, and frontal QRS-T angle, were also evaluated. These parameters were found to be valuable markers for the distribution of ventricular repolarization. Zehir et al[26] reported that the TpTe time and TpTe/QT ratio were substantially higher in patients with brucellosis than in normal. Slightly more than 90 ms of TpTec was associated with an almost threefold higher risk of sudden cardiac death[27]. TpTec

was substantially higher in the study group and five patients had more than 90 ms of TpTec. Two patients experienced non-sustained ventricular tachycardia (VT) attacks. In comparison to electrocardiographic risk indicators such as the QT period, the frontal QRS-T angle has been identified as a powerful risk predictor for cardiac morbidity and mortality[28]. While Hnutkova et al[29] determined the threshold value of the frontal QRS-T angle to be 75 degrees, Portland et al[30] calculated approximately 100 degrees. In our study, the threshold value of the frontal QRS-T angle was not determined because of the absence of mortality or sudden cardiac death. According to our findings, this parameter indicates that in patients with brucellosis, ventricular arrhythmia may increase.

Holter monitoring is the easiest method for determining if arrhythmia risk arises in patients with prolonged ECG parameters[31]. In Holter monitoring atrial arrhythmias were high and 33 (16.1%) patients in the brucellosis group had abnormal rhythms. Abnormal ST-segment and adjacent T-wave (ST-T wave) (one), sinus arrest (one), QT interval prolongation (two), complete right bundle branch block (one), first-degree AV block (two), Mobitz type 1 atrioventricular (AV) block (one), junctional tachycardia (two), non-sustained VT (two), supraventricular tachycardia (two), atrial fibrillation (three), and premature atrial contraction (seventeen) were observed in Holter recordings of the study group.

HRV is a useful indicator of the equilibrium between parasympathetic and sympathetic activity[32]. It is shown that HF, RMSSD, and pNN50 are markers of parasympathetic activity, and LF and SDNN are markers of sympathetic activity. In autoimmune diseases such as systemic sclerosis, HRV has been demonstrated to be significantly reduced in several investigations[33,34]. Anichkov et al[35] also reported impaired autonomic nervous function in febrile illness. In our study, pNN50 and RMSSD increased somewhat, but SDNN decreased significantly in the study group (p=0.096, p=0.178, and p<0.001, respectively). We observed a reduction in HF and a significant rise in LF and LF/HF ratio in patients with brucellosis, indicating that sympathetic regulation of the heart is predominant. It should also be kept in mind that high fever seen in brucellosis patients may contribute to sympathetic dominance.

Limitations

There are some limitations in our study. The study population was small. Holter monitoring was only 24-hour. In the future, an implantable loop recorder could be used. Electrophysiological studies were not conducted. Myocardial fibrosis or inflammatory diseases were not investigated with cardiac magnetic resonance imaging.

Conclusions

This study showed that brucellosis affects the cardiac conduction system and disturbs the autonomic nervous system in favor of the sympathetic nervous system. In clinical follow-ups, we can evaluate the silent cardiac involvement of brucellosis using ECG parameters, which is a non-invasive and simple method in terms of feasibility. With this method, we can prevent arrhythmias with early treatment.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Authors' Contribution

Conceptualization: Serhat Günlü (SG), Adem Aktan (AA); Data curation: SG, AA; Formal analysis: SG, AA; Funding acquisition: SG, AA; Investigation: SG, AA; Methodology: SG, AA; Project administration: SG, AA; Resources: SG, AA; Software: SG, AA; Supervision: SG, AA; Validation: SG, AA; Visualization: SG, AA; Roles/Writing - original draft: SG, AA; Writing - review and editing: SG, AA.

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Ethics Approval

The Local Ethics Committee approved the study protocol (Gazi Yaşargil Training and Research Hospital; No. 2022-22, February 11, 2022), and it followed the Declaration of Helsinki's Ethical guidelines for human testing (2013).

Availability of Data and Materials

Data are available upon reasonable request to the corresponding author. De-identified data might be available after the consent of all authors and the privacy policy of the Cizre State Hospital.

ORCID ID

Serhat GÜNLÜ: 0000-0001-6985-6112
Adem AKTAN: 0000-0003-0505-9784

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