Electrocardiographic Evaluation of Patients with Crimean-Congo Hemorrhagic Fever

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Abstract: Infectious diseases can affect the myocardium directly or through cytokines. Disruption of cardiac depolarization and repolarization is associated with the development of arrhythmia. In this study, we aimed to evaluate electrocardiographic (ECG) parameters in patients with Crimean-Congo Hemorrhagic Fever (CCHF). 42 patients hospitalized with the diagnosis of CCHF were included in the study. Heart rate, PR interval, P dispersion, QRS duration, QT interval and corrected QT, T peak T end, Tp-e/QT ratio, Tp-e/QTc ratio, and QT dispersion parameters were calculated from 12-lead ECGs at the time of admission and discharge. The mean age of the patients in the study was 45.8±16.9 years. ECG parameters were found to be similar at admission and discharge (all p values>0.1). Major events such as life-threatening bleeding, significant hypotension, and shock were not observed in any of the patients. Platelet and white blood cell values were significantly increased at discharge compared to admission (78.3 vs 197.6 x103, p=0.01 and 2.8 vs 5.4 x103, p=0.006 respectively). In patients with CCHF, there was no significant change in ECG polarization parameters at the onset of the active infection process and during hospitalization period and these parameters found to be within normal limits. ©2023 NTMS.

Keywords: Crimean-Congo Hemorrhagic Fever, electrocardiography, Tp-e, Tp-e/QT, P dispersion

1. Introduction
Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic fever caused by the nairovirus infection transmitted by tick bites, crushing infected ticks, or contact with viremic blood and tissues 1-3. It is...
now endemic in many different regions of Africa, Asia, and Eastern Europe. The most important clinical features are fever and in the most severe cases, shock and hemorrhage. As in other viral diseases, cardiac involvement may occur in CCHF and cardiac involvement may have a role in the pathogenesis of shock and may also influence the prognosis. Myocardial damage is associated with the severity of the disease, and it has been shown that cardiac dysfunction may occur in severe and fatal cases of CCHF. The direct effect of the virus or cytokine-mediated hyperinflammatory response may play a role in myocardial damage in viral infections as in the CCHF. 38% of CCHF cases have a severe course and the mortality is between 10-30%. 1-3

Many methods such as blood tests (troponin, and creatine phosphokinase), electrocardiography (ECG), echocardiography (ECHO), cardiac magnetic resonance imaging (MRI) and cardiac biopsy can be used in demonstrating the development of myocardial damage. Among these tests, ECG plays an important role because it is inexpensive, noninvasive, reproducible, can be performed practically at the bedside, and results in a short time. ECG is an important test to see arrhythmias in patients but it is not clear whether this myocardial involvement causes atrial and ventricular arrhythmias in this patient group. QT and corrected QT (QTc) intervals, QT dispersion and T peak-T end (Tp-e) which are indicators of electrocardiographic depolarization and repolarization distribution, are associated with the development of ventricular arrhythmias. P-wave dispersion reflects the prolongation of intra and inter-atrial conduction time and is associated with the development of atrial arrhythmias. To our knowledge, the literature presents no studies examining the atrial and ventricular parameters in the ECG and the development of arrhythmias related to these parameters in CCHF patients. In our study, we aimed to evaluate these electrocardiographic parameters in CCHF patients.

2. Material and Methods
2.1. Study Population
Patients hospitalized with suspected CCHF in the infectious diseases clinic between April 2020 and September 2020 were included in the study. The definitive diagnosis of CCHF infection was established by the typical clinical and epidemiological findings, in addition to the detection of CCHF-specific IgM by ELISA method or detection of the genomic segments of the virus by the reverse transcription-polymerase chain reaction (RT-PCR) method. Patients with no definitive diagnosis of CCHF were excluded from the study. The study population consisted of 42 CCHF patients with a definite diagnosis and all were hospitalized for treatment. Patients with heart failure, coronary artery disease, chronic renal failure, those using antiarrhythmic drugs, and patients with a history of arrhythmia and conduction disorder were excluded from the study. The study protocol was approved by the local institutional ethics committee, and written informed consent was received from each patient.

2.2. Electrocardiographic analysis
For electrocardiographic examination, 12-lead ECG (20 mm/mV and 50 mm/s) records at admission and before discharge were used. (Cardiofax V, Nihon Kohden Corp., Tokyo, Japan) PR interval, QRS duration, heart rate, QT interval and QTc were recorded. The QT interval was defined as the time from the beginning of the QRS complex to a point at the T-wave returned to the isoelectric line. The R-R interval was measured by averaging the time between three QRS complexes. Using this interval we calculate the heart rate and QTc interval with Bazett's formula. Patients with low-amplitude T-waves and U waves in their electrocardiograms were excluded from the study. QT dispersion was defined as the difference between the maximum and minimum QT duration recorded in all leads in ECG. The Tp-e interval can be measured using both the tail and tangent methods, but the tail method has been shown to provide a better prediction of mortality than the tangent method. Therefore, we used the tail method in the present study. According to this method, Tp-e interval was defined as the time from the peak of T-wave to the end of T-wave to a point where it reaches the isoelectric line. The Tp-e interval was measured from the V2 and V5 leads. Tp-e/QT ratios, and Tp-e/QTc ratios were calculated from these measurements. P wave dispersion was defined as the difference between the maximum and minimum P wave duration recorded in all leads in ECG. All the measurements were calculated by two independent cardiologists.

2.3. Treatment
Treatment for CCHF is primarily supportive. Treatment includes oxygenation and hemodynamic support, fluid balance and correction of electrolyte abnormalities, managing bleeding complications and appropriate treatment of secondary infections. Also intravenous immunoglobulin (IVIG) treatment can be given in patients with a poor clinical course. However, there were no patients who received IVIG treatment in our study. Therefore, in our cohort there were no patients who received any drugs causing ECG changes.

2.4. Statistical analysis
All statistical analyses were made by using the SPSS software (Version 22.0, SPSS, Inc., Chicago, IL). Visual (histograms, probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk test) were used to determine whether the variables were normally distributed. Continuous variables were presented using mean±standard deviations. Wilcoxon test was used to compare the differences of the CCHF patients’ admission and discharge parameters. Chi-square test was used to compare categorical variables. P value<0.05 was considered statistically significant.
3. Results

The mean age of the patients in this study was 45.8±16.9 years. Six (14.3%) of the patients were female. Mean hospitalization duration was 6.3±1.6 days. Four patients (9.5%) had hypertension and 3 patients (7.1%) had diabetes. These four patients were not using antiarrhythmic drugs. Major events such as life-threatening bleeding, significant hypotension and shock were not seen in any of the patients. The average body temperature was 37.2±0.8 °C at admission. Mean troponin and International Normalized Ratio (INR) values at admission were 1.12±0.3, and 4±2.2 ng/dl, respectively, and were within normal limits. All patients received symptomatic and supportive treatment. Additional platelet replacement and/or antiviral therapy and/or whole blood replacement were performed if clinically indicated. Mean platelet and white blood cell counts increased significantly at discharge when compared to admission (78.3 vs 197.6x10³, p=0.01; 2.8 vs 5.4x10³, respectively, p=0.006).

Hemoglobin level at admission was similar to discharge (13.3 vs 13.6 mg/dl, p=0.772). Serum sodium, potassium, calcium, magnesium and creatinine levels were within normal limits and were similar at admission and discharge (Table 1).

In electrocardiographic measurements heart rate (73.9 vs 68.1 bpm, p=0.233), PR interval (150 vs 149.3 msec, p=0.803), P wave dispersion (30.7 vs 30 msec, p=0.739), QRS duration (89.3 vs 90.7 msec, p=0.414), QT interval (381.4 vs 398.6 msec, p=0.155), QTc interval (417.6 vs 422.4 msec, p=0.900), lead V2 Tp-e (87.9 vs 88.6 msec, p=0.796), lead V5 Tp-e (78.6 vs 84.3 msec, p=0.103), lead V2 Tp-e/QT (0.23 vs 0.22, p=0.272), lead V5 Tp-e/QT (0.20 vs 0.21, p=0.249), lead V2 Tp-e/QTc (0.22 vs 0.21, p=0.226), lead V5 Tp-e/QTc (0.19 vs 0.20, p=0.124), and QT dispersion (33.5 vs 26 msec, p=0.132) values were similar at admission vs discharge and the values were within normal range (Table 2).

4. Discussion

In our study, atrial and ventricular ECG parameters did not change and arrhythmia was not observed at the onset of active infection and during hospitalization in patients with Crimean-Congo Hemorrhagic Fever. In addition, these parameters remained within normal limits throughout the active infection and at discharge. Myocardial involvement in CCHF patients can affect

Table 1: Admission and discharge laboratory findings of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Admission (n=42)</th>
<th>Discharge (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Temperature (°C)</td>
<td>37.2±0.8</td>
<td>36.3±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.86±0.38</td>
<td>0.77±0.16</td>
<td>0.285</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>133.9±3.1</td>
<td>133.2±2</td>
<td>0.100</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>3.8±0.35</td>
<td>4±0.34</td>
<td>0.181</td>
</tr>
<tr>
<td>Serum calcium, mg/dL</td>
<td>8.6±1.7</td>
<td>8.4±1.3</td>
<td>0.374</td>
</tr>
<tr>
<td>Serum magnesium, mg/dL</td>
<td>1.6±0.25</td>
<td>1.9±0.27</td>
<td>0.073</td>
</tr>
<tr>
<td>WBC, x 10³/mm³</td>
<td>2.8±1.3</td>
<td>5.4±1.7</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Platelets, 10⁹/mm³</td>
<td>78.3±55.3</td>
<td>197.6±63.7</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.3±4.2</td>
<td>13.6±1.4</td>
<td>0.772</td>
</tr>
</tbody>
</table>

Abbreviations: WBC: white blood cell.

Table 2: Admission and discharge electrocardiographic findings of the study population.

<table>
<thead>
<tr>
<th>ECG Variables</th>
<th>Normal values</th>
<th>Admission (n=42)</th>
<th>Discharge (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>60-100</td>
<td>73.9±14</td>
<td>68.1±8.7</td>
<td>0.233</td>
</tr>
<tr>
<td>PR interval, msec</td>
<td>120-200</td>
<td>150±19.2</td>
<td>149±20.9</td>
<td>0.803</td>
</tr>
<tr>
<td>P wave dispersion, msec</td>
<td>&lt;36</td>
<td>30.7±11.4</td>
<td>30±10.4</td>
<td>0.739</td>
</tr>
<tr>
<td>QRS duration, msec</td>
<td>70-100</td>
<td>89.3±7.3</td>
<td>90.7±8.3</td>
<td>0.414</td>
</tr>
<tr>
<td>QT, msec</td>
<td>350-450</td>
<td>381.4±48</td>
<td>398.6±36.9</td>
<td>0.155</td>
</tr>
<tr>
<td>QTc, msec</td>
<td>350-450</td>
<td>417.6±33.8</td>
<td>422.4±34.4</td>
<td>0.900</td>
</tr>
<tr>
<td>QT dispersion, msec</td>
<td>10-71</td>
<td>33.5±11.5</td>
<td>26±12.1</td>
<td>0.132</td>
</tr>
<tr>
<td>Tp-e lead V2, msec</td>
<td>50-100</td>
<td>87.9±13.7</td>
<td>88.6±10.3</td>
<td>0.796</td>
</tr>
<tr>
<td>Tp-e lead V5, msec</td>
<td>50-100</td>
<td>78.6±8.6</td>
<td>84.3±10.2</td>
<td>0.103</td>
</tr>
<tr>
<td>Tp-e/QT, lead V2</td>
<td>0.13-0.29</td>
<td>0.23±0.04</td>
<td>0.22±0.02</td>
<td>0.272</td>
</tr>
<tr>
<td>Tp-e/QT, lead V5</td>
<td>0.13-0.29</td>
<td>0.20±0.02</td>
<td>0.21±0.03</td>
<td>0.249</td>
</tr>
<tr>
<td>Tp-e/QTc, lead V2</td>
<td>0.11-0.28</td>
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<td>Tp-e/QTc, lead V5</td>
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<td>0.20±0.02</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Abbreviations: ECG: electrocardiography, QTc: rate-corrected QT interval, Tp-e: T wave peak-to-end interval.
the course and severity of the disease. As in other viral myocardial infections, this may be caused by the direct effect of the infecting virus on cardiac tissues, the attack of immune cells against infected cardiomyocytes, or cytokine-mediated damage.

Electrocardiographic and echocardiographic myocardial impairment has been shown to be related to mortality due to CCHF. ECG is not a part of the routine clinical follow-up of CCHF patients, but it has been shown that ECG changes may have a potential role in predicting disease mortality. Studies have shown that electrocardiographic (ECG) T-wave inversion, bundle branch block and echocardiographic left ventricular wall motion abnormality and pericardial effusion can be observed even in non-critical patients.

In this study, we aimed to investigate the changes in ECG parameters and the development of arrhythmia in CCHF patients and to evaluate the suitability of ECG as a routine screening test. It is not clearly known whether myocardial involvement contributes to the development of atrial or ventricular arrhythmias in these patient groups. It may be concluded that in these patient groups for whom arrhythmia has not been reported yet, ECG changes may be predictive of the severity and mortality of the disease rather than the development of arrhythmia. Considering the literature, the fact that atrial and ventricular ECG parameters, which may predict the development of arrhythmia, have not been studied before, makes our study valuable. The additional contribution of ECG to the routine follow-up of these patients is also controversial. QRS duration, QT interval and QTc, Tp-e, Tp-e/QTc, QT dispersion, which are indicators of electrocardiographic ventricular depolarization and repolarization, did not change in our patient population at admission and discharge. In addition, P wave dispersion, which is a sign of atrial conduction delay, and PR distance, which is an indicator of atrioventricular conduction duration, were also within normal limits and were similar at admission and discharge. As a result of these findings, it can be thought that this patient group are not prone to the development of atrial and ventricular arrhythmias during the active phase of the disease. In addition, troponin levels, which are indicative of myocardial damage, were also within normal limits in the whole group. Serum electrolyte levels may also affect myocardial depolarization and repolarization in CCHF patients. Electrolyte abnormality may develop and impair myocardial electrical distribution in cases such as hypotension, acute renal failure and shock. In our patient group, major events such as life-threatening bleeding, hypotension and shock, electrolyte abnormality or acute renal failure were not observed. The low platelet levels of the patients at admission reached normal levels with platelet replacement and supportive treatments. Also, the low white blood cell count at admission increased before discharge. Bradyarrhythmia may occur in approximately 4% of CCHF patients. The mechanism of this situation, which is mostly temporary, is not clear. It has also been suggested that it may develop through direct myocardial injury or cytokine induced. In our study, the mean heart rate was 73.9 bpm at admission and 68.1 bpm at discharge, and only 3 (7.1%) patients had asymptomatic sinus bradycardia and persisted at discharge.

It has been reported in the literature that viral hemorrhagic fever virus infections such as Hantavirus infection, Lassa fever, and dengue fever can cause electrocardiographic changes. Although non-specific ECG abnormalities such as ST segment and T wave changes and ST-segment elevation have been detected in Lassa fever infection, it has been revealed that these changes are not related to the clinical severity of the disease. Sinus bradycardia and conduction defects were observed in dengue fever infection, and these changes were reported to be usually temporary. In addition, ECG abnormalities have been reported in hemorrhagic fever with renal syndrome (HFRS) caused by Hanta virus. However, it has been reported that ECG changes in HFRS occur in critically ill patients, especially in the oliguric stage. Among these ECG abnormalities, prolonged QT interval, long and sharp T waves and bradycardia are more prominent. It was thought that secondary causes such as hypopituitarism, hyperthyroidism and renal failure that may increase the severity of the disease in HFRS may explain the ECG abnormalities. As a result of these findings, it can be interpreted that severe ECG changes in viral hemorrhagic fever virus infections occur during the critical stages of disease. In our study, it was observed that the parameters that can be accepted as electrocardiographic findings of atrial and ventricular arrhythmia did not change during admission and discharge.

## 5. Conclusions

Atrial and ventricular electrocardiographic parameters were in normal limits and did not change at the onset of active infection and during hospitalization in patients with Crimean-Congo Hemorrhagic Fever. The benefit of routine ECG follow-up in this patient group for determining myocardial involvement and arrhythmia seems controversial. The use of ECG can be considered in selected patient groups in order to determine cardiac involvement in patients with a poor clinical course. However, studies evaluating ECG parameters in patient groups with severe clinical course and/or mortality with proven myocardial involvement are needed.

## Limitations of the Study

The main limitation of our study was the small number of patients. We evaluated myocardial involvement only by troponin level and patients were not routinely performed echocardiography. The inability to compare with MRI and/or cardiac biopsy, which are more sensitive methods in detecting myocardial damage, is another limitation of our study. Failure to observe a clinical major adverse event in our patient group during...
follow-up led to the absence of a serious patient group. Considering that prominent ECG changes occur in patient groups with hemodynamic disorders and secondary clinical aggravation, this may be considered as a limitation.

Acknowledgement
None.

Conflict of Interests
All authors declare there is no conflict of interest.

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Author Contributions
E.A, M.Ö and S.I.Y. conceived and planned the hypothesis and wrote the manuscript. O.E.T. and G.C. performed the calculations. H.A. and Ö.K. are responsible for the data and supervised data analyses. All authors supported writing of the manuscript. E.A, M.Ö and S.I.Y. designed and directed the current topic. All authors provided critical feedback and helped shape the research, analysis and manuscript. E.A directed the final version and is responsible for final approval of the submitted manuscript.

Ethical Approval
Ethical committee approval was received from the Ethics Committee of Erzurum Region Training and Research Hospital (Approval Date: 2020; Approval Number: 2020/17-183).

Data sharing statement
All data relevant to the study are included in the article

Consent to participate
All participants read the consent form and understand the study being described.

Informed Statement
Informed consent was obtained from all participants included in the study.

References


https://dergipark.org.tr/tr/pub/ntms