Evaluation of Tp-e Interval and Tp-e/QT Ratio in Patients with Chronic Hepatitis B

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Abstract: Chronic hepatitis B (CHB) is a chronic inflammatory viral disorder. Several studies have suggested that the interval from the peak to the end of the electrocardiographic T wave (Tp-e) may correspond to the transmural dispersion of repolarisation and that increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. Impaired autonomic function has been described in patients with CHB. The aim of this study was to evaluate ventricular repolarisation by using Tp-e interval and Tp-e/QT ratio in patients with CHB, and to assess the relation with inflammation. Fifty-five patients with CHB and 50 controls were included. Tp-e interval and Tp-e/QT ratio were measured from the 12-lead electrocardiogram, and Tp-e interval corrected for heart rate. These parameters were compared between groups. In electrocardiographic parameters analysis, QT dispersion (QTd) and corrected QTd were significantly increased in CHB patients compared to the controls (38.3 ± 10.9 vs. 28.5 ± 7.3 milliseconds and 39.5 ± 11.2 vs. 29.6 ± 7.6 milliseconds, P=0.01 and P<0.001, respectively). cTp-e interval and Tp-e/QT ratio were also significantly higher in CHB patients (85.3 ± 8.2 vs. 74.5 ± 7.4 milliseconds and 0.24 ± 0.02 vs. 0.18 ± 0.02, all P-value < 0.001). Our study revealed that Tp-e interval and Tp-e/QT ratio were increased in CHB patients.

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Introduction

The hepatitis B virus (HBV) infection is a major public health problem worldwide. Hepatitis B is an infectious disease, associated with an estimated 350 million chronically infected patients (Fattovich, 2003; Lavanchy, 2004).

It is known that chronic HBV and hepatitis C virus (HCV) infection triggers autoimmune disorders. As many as 20% of patients with HBV infection experience a spectrum of extrahepatic disorders that includes dermatologic disease, polyarthralgias and arthritis, glomerulonephritis, polymyositis, aplastic anemia, neuropathy, vasculitis and myocarditis. Recent studies revealed that the virus has extensive reservoirs of extrahepatic replication. HBV proteins and nucleic acids have been found in a number of non-hepatic tissues including lymph nodes, spleen, bone marrow, kidney, colon, stomach, periadrenal ganglia, skin, thyroid, pancreas, testis, ovaries, brain, heart and lung tissue (Matsumori, 2001; Rong et al., 2007).

Cardiovascular autonomic dysfunction has been described in both chronic alcoholic and non-alcoholic liver diseases, including primary biliary cirrhosis and chronic hepatitis C virus infection (Frith and Newton, 2009; Osztovits et al., 2009). Recently we found autonomic dysfunction using heart rate variability (HRV) in patient with chronic hepatitis B (CHB) (Demir and Demir, 2012a).

Several studies reported that overall mortality of the patients with viral hepatitis such as HCV was higher than control. Although the causes underlying this increased incidence of cardiovascular disease and mortality are not entirely understood, chronic inflammatory state and autoimmunity might be related to the development of cardiovascular disease (Matsumori et al., 1998).

Myocardial repolarisation has been evaluated by various methods including QT dispersion (QTd), corrected QT dispersion (cQTd), and transmural dispersion of repolarisation (Antzelevitch et al., 1998). Recent studies indicated that Tp-e interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), can be used as an index of total (transmural, apico-basal, and global) dispersion of repolarisation (Antzelevitch et al., 2007; Kors et al., 2008). Also, increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality (Castro Hevia et al., 2006; Smetana et al., 2011). However, the Tp-e interval is affected by variations of body weight and heart rate (Gupta et al., 2008). Recently, a new index, the Tp-e/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarisation compared to QTd, cQTd, and Tp-e intervals which is independent of alterations in heart rate (Gupta et al., 2008; Zhao et al., 2012).

The aim of this study was to evaluate repolarisation dispersion measured from the 12-lead surface electrocardiogram (including Tp-e interval and Tp-e/QT ratio) in patients with CHB.

Material and Methods

Study population

55 patients mean age was 35 ± 9 years (range 20–65 years), who has been followed in the outpatient clinic of infection diseases department because of the CHB (HbsAg positive, anti-HBs negative for at least 6 months), has normal liver enzymes and has not received antiviral treatment, are included in the study.

The control group was consisted of 50 successive persons, mean age was 29 ± 13 years (range 19–53 years), who appealed to the cardiology outpatient clinic because of various reasons and did not have any structural cardiac pathologies identified.

Physical examination, medical history of patients, and blood biochemistry were evaluated in all groups to exclude systemic diseases. Patients with coronary artery disease, heart failure, valve disease, cardiomyopathy, hypertension, diabetes mellitus, chronic lung disease, hepatic and renal dysfunction, thyroid dysfunction, anaemia, electrolyte imbalance, bundle branch block, atrioventricular conduction abnormalities on ECG and ECGs without clearly analysable QT segment were excluded from the study. The study did not include intravenous drug abusers, alcohol drinkers, HIV and hepatitis C virus carriers. All of the patients were in sinus rhythm and none of them were taking cardioactive medications like antiarrhythmics, antipsycotics, and antihistaminics.

Electrocardiography

The 12-lead ECG was recorded at a paper speed of 50 mm/s (Nihon Kohden, Tokyo, Japan) at rest in the supine position. Resting heart rate was measured from the ECG taken during the patient evaluation. To decrease the error measurements, QT and Tp-e intervals were measured manually with calibres and magnifying glass. Subjects with U waves on their ECGs were excluded from the study. An average value of three readings was calculated for each lead. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and was corrected for heart rate using the Bazett formula: $cQT = QTd\surd$ (R–R interval). The QTd was defined as the difference between the maximum and minimum QT interval of the 12-leads (Day et al., 1990). The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave, and was corrected for heart rate. Measurements of Tp-e interval were performed from precordial leads (Castro Hevia et al., 2006). Tp-e/QT ratio was calculated from these measurements.

Statistical analysis

SPSS 16.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for statistical study. All values are given as mean ± standard deviation. Mean values of continuous variables were compared between groups using the Student's *t*-test or Mann-Whitney U test, according to whether normally distributed or not, as tested by

the Kolmogorov-Smirnov test. The chi-square test was used to assess differences between categorical variables. Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables. A P-value of less than 0.05 was considered significant.

Results

Clinical characteristics and echocardiographic findings of the two groups are shown in Table 1. Age, sex, body mass index, smoking status, systolic and diastolic blood pressure, rest heart rate, left ventricular (LV) end-diastolic dimension, LV end-systolic dimension, left atrium dimension, and LV ejection fraction were similar between the two groups (P>0.05).

Table 1 – Comparison of clinical and echocardiographic features of CHB patients and controls

	CHB (n=55)	Controls (n=50)	P-value
Age (years)	35 ± 19	29 ± 13	NS
Male/female (n/n)	26/24	20/30	NS
BMI (kg/m^2)	23 ± 5	26 ± 6	NS
LA diameter(cm)	3.3 ± 0.9	3.2 ± 0.6	NS
LV EDD (cm)	4.6 ± 1.5	4.3 ± 0.5	NS
LV ESD (cm)	2.7 ± 0.7	2.8 ± 1.2	NS
SBP (mm Hg)	123 ± 11	121 ± 6	NS
DBP (mm Hg)	77 ± 14	75 ± 9	NS
Smoking (n)	9	9	NS

CHB – chronic hepatitis B; BMI – body mass index; LA – left atrium; LV EDD – left ventricular end-diastolic dimension; LV ESD – left ventricular end-systolic dimension; SBP – systolic blood pressure; DBP – diastolic blood pressure; NS – nonsignificant

Table 2 – Comparison of electrocardiographic features of CHB patients and controls

	CHB (n=55)	Controls (n=50)	P-value
QT dispersion (QTd) (ms)	38.3 ± 10.9	28.5 ± 7.3	0.001
Corrected QT dispersion (cQTd)	39.5 ± 11.2	29.6 ± 7.6	<0.001
Corrected Tp-e interval	85.3 ± 8.2	74.5 ± 7.4	<0.001
Tp-e/QT ratio	0.24 ± 0.02	0.18 ± 0.02	<0.001

CHB – chronic hepatitis B

Electrocardiographic parameters of the groups are shown in Table 2. QTd and corrected QTd were significantly increased in CHB patients compared to the

controls (38.3 ± 10.9 vs. 28.5 ± 7.3 milliseconds and 39.5 ± 11.2 vs. 29.6 ± 7.6 milliseconds, P=0.01 and P<0.001, respectively). cTp-e interval and Tp-e/QT ratio were also significantly higher in CHB patients (85.3 ± 8.2 vs. 74.5 ± 7.4 milliseconds and 0.24 ± 0.02 vs. 0.18 ± 0.02, all P-value < 0.001).

Discussion

The present study showed that Tp-e interval and Tp-e/QT ratio were prolonged in patients with CHB when compared to the controls.

CHB is a systemic chronic inflammatory disorder. Also, multiple extrahepatic manifestations of HBV have been recognized. Several previous studies revealed that cardiac involvement such as left and right ventricular systolic function abnormalities (Demir and Demir, 2012b), evidence of atherosclerosis (Amirzadegan et al., 2007), and cardiac autonomic dysfunction (Demir and Demir, 2012a) have been described in these patients. In addition, increased cardiovascular morbidity and mortality have been demonstrated in patients with viral hepatitis when compared to the controls in previous studies (Matsumori et al., 1998; Weber et al., 2010). Wang et al. (2011) were found higher NT-proBNP levels, increasing with the heart failures in the HBV/HCV patients not having liver failure, in comparison with the control group. Similarly Kucukazman et al. (2012) were found higher BNP levels in asymptomatic HBV positive patients.

In our study we have found significantly differences in QTd and cQT between CHB patients and control group. Also, our findings are consistent with those of Matsumori et al. (1998) that frequencies of atrial and ventricular arrhythmias were increased in HCV patients than controls.

Increased dispersion of repolarisation, the disturbance of the normal orderly pattern of ventricular recovery, is generally thought to predispose to ventricular arrhythmias. Recently, the Tp-e interval and Tp-e/QT ratio have emerged as novel electrocardiographic markers of increased dispersion of ventricular repolarisation (Gupta et al., 2008; Kors et al., 2008). Also, these markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death. Tp-e/QT ratio was reported as a more accurate marker for ventricular arrhythmogenesis compared to Tp-e interval and QTd due to independency of heart rate. Previous studies showed that prolongation of Tp-e interval was associated with increased mortality in Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, and in patients undergoing primary percutaneous coronary intervention for myocardial infarction (Castro Hevia et al., 2006; Smetana et al., 2011; Zhao et al., 2012).

Our results may contribute to pathophysiological mechanisms of increased prevalence of ventricular arrhythmias and cardiovascular mortality risk by indicating increased ventricular repolarisation heterogeneity in these patients.

There is limited data evaluating Tp-e interval and Tp-e/QT ratio in other systemic inflammatory diseases. It has been reported that transmural dispersion

of repolarisation is increased in Ankylosing spondylitis, nondipper hypertension patients (Acar et al., 2013; Demir and Uyan, 2013). Tp-e interval and Tp-e/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias in patients with CHB.

Limitations
The most significant limitation of our study is the insufficient number of the patients. Other limitations of our study are that our study is not prospective and does not include anti-HBc levels showing active infection, and an unknown duration of HBV infection. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Therefore, we could not evaluate the potential prognostic role of the electrocardiographic ventricular repolarisation indexes with respect to future untoward events. For this reason, long-term follow-up and large-scale prospective studies are needed to determine the predictive value of prolonged Tp-e interval and increased Tp-e/QT ratio in this population. Finally, manual measurement of QT and Tp-e intervals on paper-printed electrocardiogram might have underpowered the results because it would be more reliable if measured on the high-resolution screen of a digital system.

Conclusion
Our study revealed that Tp-e interval and Tp-e/QT ratio were increased in CHB patients. Tp-e interval and Tp-e/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias in patients with CHB.

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