Effect of hepatitis B virus infection on right and left ventricular functions

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Summary

Background: In this study we examined right and left ventricular systolic functions in hepatitis B virus (HBV) patients.

Material/Methods: The study included 50 HBsAg-positive patients (mean age: 33±13 years) and 50 other persons (mean age: 28±11 years) as a control group. Transthoracic echocardiography was performed in all the participants. Right and left ventricle systolic parameters were compared between these 2 groups.

Results: In the group of the patients with HBsAg positivity, the right ventricular fractional area change (RV FAC), tricuspid annular plane excursion (TAPSE) and RV myocardial systolic velocity (St) values were lower than in the control group (33±11 vs. 52±13%, p=0.001; 14.6±1.1 vs. 22.2±2.4 mm, p<0.001; 8.6±1.2 vs. 15.8±2.3 cm/s, p<0.001, respectively); the right atrium (RA) and RV diameters were higher than in controls (5.1±1.2 vs. 3.7±0.5 cm, p<0.001; 4.9±0.8 vs. 3.4±0.5 cm p<0.001, respectively); and systolic pulmonary artery pressure was higher than in control (39.3±9.5 vs. 22±8.4 mmHg, p<0.001).

Conclusions: The findings showed that HBV infection may be associated with right ventricular systolic dysfunction and pulmonary hypertension.

key words: hepatitis B virus • cardiomyopathy • myocarditis • pulmonary artery hypertension

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Background

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 [1,2].

HBV is a 42-nm DNA virus in the family Hepadnaviridae. The virus has a partially double-stranded DNA with core antigen surrounded by a shell containing surface antigen (HBsAg). Antibody to HBsAg (anti-HBs) appears after clearance of HBsAg or after immunization. The presence of HBsAg for more than 6 months is defined as chronic HBV infection [3].

The clinical course of HBV infection is determined by the interaction of viral replication status and host immune response. HBV infection is generally asymptomatic, but HBV is the most common and important cause of cirrhosis and hepatocellular carcinoma worldwide [2,4].

Chronic HBV and hepatitis C virus (HCV) infection trigger 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. Recently, HBV replication was found in damaged endothelial tissues of patients with extrahepatic disease, which indicates that endothelial tissues may be one of the tropism tissues infected by HBV in extrahepatic disease [5–8].

Several viruses, mainly HHV-6, parvovirus B19, adenoviruses and enteroviruses, may infect the myocardium. Since these agents cannot be found in many patients with myocarditis, other etiologic agents have been searched for. Recently, there has been recognition of the recognized significance of HCV infection in hypertrophic or dilated cardiomyopathy and myocarditis patients [9–13]. Moreover, we have determined a relation between HCV infection and LV systolic and diastolic dysfunction and LV hypertrophy in our previous studies [14,15].

It is also thought that there is a relation between HBV and coronary artery disease. Conflicting findings on the possible association between HBsAg-positivity, indicating inactive HBsAg carrier status, and atherosclerosis have been reported [16–18]. However, there is no consensus on this issue.

To our knowledge, there has been no study evaluating right and left ventricular systolic functions in HBV patients. Our present study was conducted to investigate the effect of HBV infection on systolic functions of the right and left ventricles.

Material and Methods

Selection of the patients

The study included 50 patients, with a mean age of 33±13 years (range: 22–60 years), who were followed in the outpatient clinic of our infectious diseases department because of chronic hepatitis B infection (HBsAg-positive, anti-HBs-negative for at least 6 months), with normal liver enzymes and no antiviral treatment.

The control group was consisted of 50 successive cardiology outpatient clinic patients, mean age was 28±11 years (range: 21–55 years), seen for various reasons, and who did not have any structural cardiac pathologies identified.

We excluded from the study patients with coronary artery disease, heart failure, valve disease, cardiomyopathy, hypertension, diabetes mellitus, chronic lung disease, hepatic and renal dysfunction, thyroid dysfunction, and anaemia. 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, anti-psychotics, and antihistaminics. Every patient signed an informed consent form and the local ethics committee approved the study.

Echocardiographic measurements

Two-dimensional, M-mode, pulsed and color flow Doppler echocardiographic examinations of all subjects were performed by the same examiner with a commercially available machine (Vivid 7 pro, GE, Horten, Norway, 2–4 MHz phased array transducer). During echocardiography, a 1-lead electrocardiogram was recorded continuously.

M-mode measurements were performed according to American Society of Echocardiography criteria [18,19]. Left atrium (LA) diameter, LV end-systolic and end-diastolic diameters were measured. LV ejection fraction (EF) was estimated by Simpson’s rule.

Pulsed-wave mitral flow velocities were measured from the apical 4-chamber view by inserting a sample volume to mitral leaflet tips. Mitral early diastolic velocity (E, cm/sn), late diastolic velocity (A, cm/sn), E/A ratio, E deceleration time (DT, ms), and isovolumetric relaxation time (IVRT, ms) were determined. Each representative value was obtained from the average of 3 measurements. Doppler tissue imaging echocardiography was performed by transducer frequencies of 3.5–4.0 mHz, adjusting the spectral pulsed Doppler signal filter until a Nyquist limit of 15–20 cm/sn was reached, and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. LV myocardial peak systolic (Sm, cm/s), RV myocardial peak systolic velocity (St), isovolumetric contraction time (ICT, ms), isovolumetric relaxation time (IRT, ms), and ejection time (ET, ms) were obtained by placing a tissue Doppler sample volume in the basal segments of the lateral and septal walls of both ventricles. Myocardial performance index (MPI) was calculated using (ICT+IRT)/ET formula for LV. Mean LV Sm, mean RV St, and mean LV MPI values were obtained by calculating the arithmetical mean value of the segmental values. Therefore, the Doppler tissue velocities given represent an average of the basal segments of the lateral septal walls. The tricuspid annular motion was recorded at the right ventricle (RV) free wall for tricuspid annular plane excursion (TAPSE). RV fractional area change (FAC) was measured.
from the apical 4-chamber view according to the criteria of American Society of Echocardiography and European Association of Echocardiography [20].

**Statistical analyses**

SPSS 16.0 statistical program (SPSS, Chicago, IL, USA) was used for statistical study. All values are given as mean ± standard deviation. Values between different groups were compared using the independent-samples t-test. A Chi-squared test was used to assess differences between categorical variables. The relationship between parameters was determined using the Pearson coefficient of correlation. P-values <0.05 were considered significant.

**RESULTS**

The characteristics of both HBV and control groups are listed in Table 1. There was no statistically significant difference between HBV group and controls with regard to age, sex, diameters of the left atrium and the left ventricle, blood pressure, body mass index and smoking status.

In the HBV-positive group, the RV FAC, TAPSE and St values were found to be lower (33±11 and 52±13%, p=0.001; 14.6±1.1 and 22.2±2.4 mm, p<0.001; 8.6±1.2 and 15.8±2.3 cm/s, p<0.001, respectively); the RA and RV diameters were found to be higher (5.1±1.2 and 4.5±0.5 cm, p<0.001; 4.9±0.8 and 4.1±0.5 cm p<0.001, respectively); additionally, systolic pulmonary artery pressure (SPAP) was found to be higher (39.3±9.5 and 22±8.4 mmHg, p<0.001). No other statistically significant difference was found between the 2 groups with regard to the left ventricle systolic and diastolic parameters. There was no significant difference between the groups with respect to Sm, Em, or Am values (P>0.05). MPI, which shows both systolic and diastolic functions, was similar between the 2 groups (P>0.05) (Table 2).

**DISCUSSION**

In this study the risk of right ventricular involvement and RV systolic dysfunction in HBV patients was higher than in healthy people.

Recently, the importance of HCV infection in myocarditis and cardiomyopathy has been emphasized. HBV and HCV have been associated with atherosclerosis and HCV seropositivity in the patients with coronary artery disease, and this was found to be related to cardiac failure and increased mortality [10,22]. However, the effect of HBV on the right and left ventricle functions has not been known.

Matsumori et al. [9] found anti-HCV positivity in 10.6% of patients with hypertrophic cardiomyopathy and in 6.3% of patients with dilated cardiomyopathy. Additionally, they found arrhythmia in 21.5% of anti-HCV-positive patients; hence, the authors suggested that HCV might play a role in several cardiac disorders with formerly unidentifiable etiology.

In our previous study, an association was also found between HCV infection and left ventricular hypertrophy in terms of the left ventricular systolic and diastolic dysfunction [14,15]. There are some conflicting results in the literature about the relation between HBV and atherosclerosis and coronary artery disease [16,17,23].

Turan et al. [18] found high mean platelet volume (MPV) values, the indicator of susceptibility for atherothrombosis, in HBV patients.

**Table 1.** Comparison of clinical and echocardiographic features of HBsAg positive patients and controls group.

|                         | Patients (N=50) | Controls (N=50) | P-Value |
|-------------------------|----------------|----------------|---------|
| Age (years)             | 33±13          | 28±11          | 0.243   |
| Male/female (n/n)       | 26/24          | 20/30          | 0.260   |
| BSA (m²)                | 1.9±0.6        | 1.9±0.2        | 0.144   |
| BMI (kg/m²)             | 22±5           | 26±6           | 0.263   |
| LA diameter (cm)        | 3.3±0.7        | 3.2±0.6        | 0.762   |
| LV EDD (cm)             | 4.5±1.5        | 4.3±5.5        | 0.321   |
| LV ESD (cm)             | 2.8±0.9        | 2.6±1.2        | 0.318   |
| RA diameter (cm)        | 5.1±1.2        | 4.5±0.5        | <0.001  |
| RV diameter (cm)        | 4.9±0.8        | 4.1±0.5        | <0.001  |
| SBP (mmHg)              | 125±12         | 122±16         | 0.316   |
| DBP (mmHg)              | 76±14          | 77±9           | 0.160   |
| Smoking (n)             | 8              | 10             | 0.293   |

BSA – body surface area; BMI – body mass index; LA – left atrium; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension; RA – right atrium; RV – right ventricle; SBP – systolic blood pressure; DBP – diastolic blood pressure.
It is also suggested that HBV may lead to heart failure and cardiomyopathy, like HCV. Wang et al. [24] 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. [25] found higher BNP levels in asymptomatic HBV-positive patients, and Maha et al. [26] found LV diastolic dysfunction in patients with HCV. According to this situation, it is considered that both HBV and HCV infections may increase heart failure. However, RV systolic dysfunction is followed, although LV systolic dysfunction is not determined in the HBV patients in our study. This situation may explain the high level of NT-proBNP and BNP in these patients.

Despite a large number of studies on the relation between cardiomyopathy, myocarditis and heart failure, the data on cardiac effects of HBV is limited. In our study, we found lower RV FAC, TAPSE and St, which show RV systolic dysfunction in the patients group. Similarly, RA and RV diameters were found to be higher in the patients group.

In our first study we observed that, unlike HCV, HBV infection causes RV involvement rather than LV involvement, and pulmonary artery pressure was found to be higher than in the control group. It may be considered that this situation causes RV systolic dysfunction and portal hypertension due to the hidden liver failure. That HBV mainly affected RV rather than LV and higher PAP made us think that it might result in pulmonary HT and RV dysfunction as causes of lung disease. Moreover, there may be some bioactive substances that we have not recognized yet, which lead to obscure hepatic failure with normal AST/ALT, and consequently are not metabolized in the liver and affect only RV, but not LV, since they are metabolized in the lungs. Furthermore, hepatic failure may lead to portopulmonary HT and consequent RV dysfunction without manifesting clinical symptoms.

The most significant limitation of our study is the insufficient number of the patients. Other limitations of our study are that it was not a prospective, single transthoracic echocardiography assay and did not include anti-HBc levels showing active infection and HBV-DNA levels showing viral load and an unknown duration of HBV infection. Further tests and evaluations, except physical examination, were not performed for lung disease and sleep apnea. For hepatic failure, further evaluation other than AST, ALT and imaging studies were not performed. That matter is another limitation of our study.

### Conclusions

Our findings showed that HBV infection seems to be associated with the RV systolic dysfunction and pulmonary artery hypertension, although the mechanisms of these are not completely understood. Therefore, cardiac involvement (especially right) should be considered during the follow-up of a patient with HBV infection for extra hepatic involvement and these patients should be monitored with echocardiography. Furthermore, HBV should be kept in mind for the patients who have cardiomyopathy, right cardiac failure and pulmonary hypertension with unidentifiable etiology. Further comprehensive studies may be needed to confirm our findings.

### Table 2. Conventional echocardiographic and tissue doppler echocardiographic parameters.

| Parameter            | Patients (N=50) | Controls (N=50) | P-Value |
|----------------------|----------------|----------------|---------|
| LV EF (%)            | 61±16          | 64±11          | 0.542   |
| Mitral E velocity (cm/s) | 99.5±6     | 98.7±12        | 0.247   |
| Mitral A velocity (cm/s) | 79.2±11     | 80.2±18        | 0.365   |
| E/A                  | 1.2±0.7        | 1.23±0.2       | 0.152   |
| IVRT (ms)            | 88±9           | 82±9           | 0.322   |
| DT (ms)              | 176±15         | 182±14         | 0.625   |
| Sm (cm/s)            | 11.6±1.1       | 12.2±2.4       | 0.456   |
| E/Em                 | 7.7±2.2        | 6.8±2.3        | 0.065   |
| MPI                  | 42.2±6.7       | 41.8±7         | 0.291   |
| RV FAC (%)           | 33±11          | 52±13          | 0.001   |
| TAPSE (mm)           | 14.6±1.1       | 22.2±2.4       | <0.001  |
| St (cm/s)            | 8.6±1.2        | 15.8±2.3       | <0.001  |
| SPAP (mmHg)          | 39.3±9.5       | 22±8.4         | <0.001  |

LV EF – left ventricular ejection fraction; IVRT – isovolumic relaxation time; DT – deceleration time; Sm – mean LV systolic myocardial velocity; Em – mean LV myocardial early diastolic velocity; MPI – myocardial performance index; RV FAC – right ventricular fraction area change; TAPSE – tricuspid anular plane excursion, St – mean RV systolic myocardial velocity; SPAP – systolic pulmonary artery pressure.
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