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Original Article

Effect of hepatitis C virus infection on the right ventricular functions, pulmonary arterypressure and pulmonary vascular resistance

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Abstract: Background: Hepatitis secondary to infection with the hepatitis C virus (HCV) is one of themost common causes of viral hepatitis worldwide. Multiple extrahepatic manifestations of HCV infection have been recognized. In this study we aimed to examine right ventricular systolic functions and pulmonary artery pressure in HCV patients. Subjects and Methods: The study included 50 HCV patients (mean age; 34 ± 12 years) and 50 other persons (mean age; 28 ± 11 years) as control group. Transthorasic echocardiography was performed in all the participants. Right ventricle systolic parameters, pulmonary artery pressure, pulmonary vascular resistance (PVR) were compared between these two groups. Results: In the group of the patients with HCV, the right ventricular fractional area change (RV FAC), tricuspid annular plane excursion (TAPSE) and RV myocardial systolic velocity (St) values were lower than control group (31 ± 10 vs 48 ± 12%; 13.5 ± 1.5 vs 19.2 ± 3.4 mm and 8.3 ± 1.1 vs 17.7 ± 3.3 cm/s all $P < 0.001$, respectively); the right atrium (RA) and RV diameters were higher than controls (4.8 ± 1.3 vs 3.6 ± 0.6 cm, $P < 0.001$; 4.4 ± 0.8 vs 3.3 ± 0.5 cm $P < 0.001$, respectively); additionally systolic pulmonary artery pressure and PVR were higher than control (36.3 ± 9.9 vs 23 ± 7.8 mmHg, 3.5 ± 1.1 vs 2.1 ± 0.8; $P < 0.001$, respectively). Conclusion: The findings showed that HCV infection may be associated with right ventricular systolic dysfunction and pulmonary hypertension.

Keywords: Hepatitis C virus, cardiomyopathy, myocarditis, pulmonary artery pressure, pulmonary vascular resistance

Introductıon

The hepatitis C virus (HCV) infection is a major public health problem worldwide. Additionally, HCV infection has been associated with extrahepatic involvements such as Sjögren's syndrome, cryoglobulinemia, glomerulonephritis, lichen planus, and Hashimato's thyroiditis [1, 2]. It is also considered that there is a relation between HBV and HCV and coronary artery disease and heart failure [3-6].

Recent studies revealed that there is a relation between HCV and lung disease such as pulmonary fibrosis, chronic obstructive pulmonary disease and interstisyal pneumonitis [7, 8].

Several viruses, mainly parvovirus, adenoviruses and enteroviruses, may infect the myocardium. Since these agents cannot be found in many patients with myocarditis, other etiologic agents have been searched. Recently, the significance has been recognised of HCV infection in hypertrophic or dilated cardiomyopathy and myocarditis patients [9, 10]. Moreover, we determine a relation between HCV infection and LV systolic and diastolic disfunction and LV hypertrophy in the studies done before [6, 11].

To our knowledge, there has been no study evaluating right ventricular systolic functions and pulmonary hypertension in HCV patients. Our present study was conducted to research the effect on systolic functions of the right ventricle, pulmonary artery pressure and pulmonary vascular resistance (PVR) among the persons with HCV infection.

Methods

Selection of the patients

50 patients (mean age was 34 ± 12 years), who has been followed in the outpatient clinic

Table 1. Comparison of clinical and echocardiographic features of HCV patients and controls group

	Patients (N=50)	Controls (N=50)	*P*-Value
Age (years)	34 ± 12	28 ± 11	NS
Male (n%)	25 (50)	20 (40)	NS
BSA (m^2)	1.9 ± 0.3	1.9 ± 0.2	NS
LV EF (%)	58 ± 9	64 ± 11	NS
LA diameter (cm)	3.5 ± 0.8	3.2 ± 0.6	NS
LV EDD (cm)	4.6 ± 1.9	4.3 ± 5.5	NS
LV ESD (cm)	2.9 ± 0.9	2.5 ± 0.7	NS
E/A	1.3 ± 0.4	1.2 ± 0.2	NS
E/e'	9.1 ± 1.1	6.7 ± 0.9	NS
SBP (mmHg)	120 ± 13	122 ± 16	NS
DBP (mmHg)	74 ± 15	77 ± 9	NS
Smoking (n)	9	10	NS

BSA: body surface area, LA: left atrium, LV EF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, e': mean LV myocardial early diastolic velocity , SBP: systolic blood pressure, DBP: diastolic blood pressure.

of infection diseases department because of the chronic hepatitis C (anti-HCV and HCV-RNA positive 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 28 ± 11 years) who appealed to the cardiology and infectious disease outpatient clinic because of various reasons and did not have any structural cardiac pathologies identified.

A physical examination, the medical history of patients, and the blood biochemistry were evaluated in all groups. The subjects were defined as hypertensive if their blood pressure was ≥ 140/90 mmHg or if they were receiving any antihypertensive medication. Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage or fasting glucose level above 126 mg/dl. Smoking status was classified as smokers or those who never smoked.

Patients with coronary artery disease, heart failure, valve disease, cardiomyopathy, hypertension, diabetes mellitus, chronic lung disease, sleep apne, thyroid dysfunction, anemia, malignancy, renal and hepatic insufficiency, chronic inflammatory disease, pregnancy, septicemia, cerebrovascular accident were exluded from the study. The study did not include intravenous drug abusers, alcohol drinkers, HIV and hepatitis B virus carriers. All of the patients were in sinus rhythm and none of them were taking cardioactive medications like antiarrhythmics, antiplatelet, antipsycotics, 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 colour flow Doppler echocardioagraphic 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 one-lead electrocardiogram was recorded continuously.

M-mode measurements were performed according to the criteria of American Society of Echocardiography [12, 13]. Left atrium (LA) diameter, LV end-sistolic and end-diastolic diameters were measured. LV ejection frection (EF) was estimated by Simpson's rule.

Pulsed-wave mitral and trikuspid flow velocities were measured from the apical four-chamber view by inserting a sample volume to leaflet tips. Mitral and trikuspid early diastolic velocity (E, cm/sn), late diastolic velocity (A, cm/sn), E/A ratio, and E deceleration time (DT, ms) were determined. Each representative value was obtained from the average of three 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 optimise the spectral display of myocardial velocities. LV myocardial peak systolic (s', cm/s), early (e') and late (a') diastolic velocities and right ventricle (RV) myocardial peak systolic (St), early (RVe') and late (RVa') diastolic velocity, 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 both ventricul. Myocardial performance index (MPI) was calculated using

Table 2. Conventional and tissue doppler right ventricular echocardiographic parameters

	Patients (N=50)	Controls (N=50)	*P*-Value
RA diameter (cm)	4.8 ± 1.3	3.4 ± 0.6	< 0.001
RV diameter (cm)	4.3 ± 0.8	3.2 ± 0.5	< 0.001
RV E/A	1.1 ± 0.3	1.3 ± 0.5	NS
RV DT (ms)	186 ± 16	175 ± 14	NS
RV E/e'	9.3 ± 2.4	5.2 ± 1.5	< 0.001
RV MPI	0.47 ± 0.7	0.33 ± 0.4	< 0.001
RV FAC (%)	34 ± 11	62 ± 13	0.001
TAPSE (mm)	15.3 ± 2.1	23.4 ± 3.3	< 0.001
St (cm/s)	9.1 ± 1.1	16.2 ± 2.4	< 0.001
SPAP (mmHg)	36.3 ± 9.9	23.1 ± 8	< 0.001
PVR (Wood)	3.5 ± 1.1	2.1 ± 0.6	< 0.001

RA: right atrium, RV: right ventricul, DT: deceleration time, RV e': mean RV myocardial early diastolic velocity, MPI: myocardial performance index, RV FAC: right ventricular fractione area change, TAPSE: tricuspid anular plane excurtion, St: mean RV systolic myocardial velocity, SPAP: systolic pulmonary artery pressure, PVR: pulmonary vascular resistance.

(ICT+IRT)/ET formula for RV. By calculating the arithmetical mean value of the segmental values, mean RV St, e', a', mean MPI values were obtained. Therefore, Doppler tissue velocities given represent an average of the basal segments of the lateral septal walls. The tricuspid annular motion was recorded at the RV free wall for tricuspid annular plane excursion (TAPSE) and RV fractional area change (FAC) was measured from the apical four-chamber view according to the criteria of American Society of Echocardiography and European Associated Echocardiography [14]. PVR was calculated using (TR max velocity/RVOTVTİ) x10+0.16 [15].

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-square 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

There was no statistically significant difference between HCV group and controls with regard to age, gender, blood pressure, body surface area, smoking status, diameters of the left atrium and the left ventricle and left ventricular systolic and diastolic parameters (**Table 1**).

In HCV positive group, the RV FAC, TAPSE and St values were found to be lower (34 ± 10 vs 62 ± 13% and 15.3 ± 2.1 vs 23.4 ± 3.3 mm, and 9.1 ± 1.1 vs 16.2 ± 2.4 cm/s, all $P < 0.001$, respectively); MPI, which shows both systolic and diastolic functions, was found to be higher patients groups than control (0.47 ± 0.7 vs 0.33 ± 0.2, $P < 0.001$). The RA and RV diameters were found to be higher (4.8 ± 1.3 vs 3.4 ± 0.6 cm and 4.3 ± 0.8 vs 3.2 ± 0.5 cm both $P < 0.001$, respectively); additionally systolic pulmonary artery pressure (SPAP) and PVR were found to be higher (36.3 ± 9.9 vs 23.1 ± 8 mmHg, and 3.5 ± 1.1 vs 2.1 ± 0.8; $P < 0.001$, respectively). Also RV E/e' ratio which shows diastolic dysfunction significantly higher in the HCV patients (9.3 ± 2.4 vs 5.2 ± 1.5, $P < 0.001$). No other statistically significant difference was found between two groups with regard to the right ventricle diastolic parameters (**Table 2**).

Discussion

In this study revealed that pulmonary systolic pressure and PVR were higher in HCV patients than controls. Also there is a relationship between RV systolic dysfuction and HCV.

Recently, it has been emphasised the importance of HCV infection in myocarditis and cardiomyopathy. HBV and HCV has been associated with atherosclerosis and HCV sero-positivity in the patients with coronary artery disease and this was found to be related to cardiac failure and increased mortality [16]. Matsumori et al. found anti-HCV positivity in 10.6% of the patients with hypertrophic cardiomyopathy and in 6.3% of the 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 [17].

In our previous study, an association was also found between HCV infection and the left ventricular hypertrophy, in terms of the left ventricular systolic and diastolic dysfunction [6, 11]. Wang et al. 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 [18].

Recent studies revealed that there is a relation between HCV and lung disease such as pulmonary fibrosis, chronic obstructive pulmonary disease and interstisyal pneumonitis [7, 8].

According to this situation, it is considered that HCV infections may increase heart failure and pulmonary dysfunctions. Despite a large number of studies done about the relation between cardiomyopathy and heart faliure, the data about cardiac and pulmonar effects of HCV is limited.

In our study, we found lower RV FAC, TAPSE, St and we found higher MPI which show RV systolic dysfunction in the patients group. Similarly, E/e' ratio that shows diastolic dysfunction is significantly higher in the HCV patients.

As far as we know in our first study, it is observed that HCV infection causes RV systolic may bediastolic dysfunction. Also PASP and PVR were found higher than the control group. It may be considered that this situation causes RV systolic dysfunction, pulmonary dysfunction and portal hypertension due to the hidden liver failure. 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 our study is not prospective, single transthoracic echocardiography assay. 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 restriction of our study.

In conclusion, our findings showed that HCV infection seemed to be associated with the RV systolic dysfunction and pulmonary artery hypertension although the mechanisms of these are not known thoroughly. Therefore, cardiac involvement and pulmonary hypertension should be considered during the follow-up of a patient with HCV infection for extra hepatic involvement and these patients should be monitored with echocardiography. Furthermore, HCV 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.

Disclosure of conflict of interest

None.

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