Detection of Subclinical Right Ventricular Dysfunction in Patients with Hepatitis C Virus Infection by Speckle Tracking Echocardiographic Assessment

Islam Z. Mahmoud*, Ahmed H. Abdel-Moneim, Hesham H. Ali, Enas A. Ismail

Department of Cardiology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Abstract

Background: **Hepatitis C virus (HCV) infection is associated with cardiac dysfunction, affecting patients' morbidity and mortality. This study aimed at assessing whether myocardial deformation indices by two- (2D) and three-dimensional (3D) speckle tracking echocardiography can be used as an early imaging biomarker of right ventricular (RV) function affection in HCV patients even in early stages without significant hepatic cirrhosis.** ***Subjects and Methods:*** **54 HCV patients were recently diagnosed by PCR and classified as Child Paugh A without previous cardiovascular events, and 54 matched healthy controls were enrolled. RV function was assessed using the transthoracic echocardiography conventional and advanced deformation assessment by speckle tracking including global longitudinal and segmental strain.** ***Results:*** **All conventional parameters resulted in the normal range without significant differences between HCV and controls including RIMP, TAPSE, FAC, and S' velocity (P value: 0.41, 0.11, 0.74, and 0.11, respectively). Only the apical RV free wall segment longitudinal strain by speckle tracking was more impaired than controls (-19.19 ± -7.23 vs. -21.64 ± -2.07, P value: <0.001). At the same time, the Global longitudinal strain (-24.2 ± -4.91% vs. -24.98 ± -2.61%, p = 0.171) was similar in both groups.** ***Conclusion:*** **Speckle tracking can detect subclinical RV dysfunction in HCV patients even with normal baseline conventional parameters.**

Keywords: Hepatitis C Virus: Right ventricular dysfunction; RV Speckle tracking.

Introduction

Hepatitis C virus (HCV) infection is a major health burden in Egypt, where it bears the highest prevalence rate in the world[1]. Recent studies have shown a decreasing prevalence of HCV worldwide. Despite its long-term resultant consequences, it is still a major endemic health problem among the Egyptian population[2]. In Egypt, in the 15–59-year age group, the prevalence of HCV antibody was found to be 10.0%. Approximately, 3.7 million persons had chronic HCV infection in the age group 15–59 in 2015[3]. Beyond the liver, HCV chronic infection leads to a multifaceted systemic disease. Those include vasculitis, B-cell lymphoproliferative diseases, arthralgia, sicca

*Corresponding Author: islam.z.mahmoud@med.suez.edu.eg

syndrome, renal insufficiency, insulin resistance and type 2 diabetes, fatigue, depression, and cognitive[4]. Many studies evaluated the frequency and characteristics of cardiovascular involvement in HCV patients. Those patients have an increased prevalence of carotid atherosclerosis and increased intima-media thickness compared to healthy controls. Active chronic HCV infection appears as an independent risk factor for ischemic cerebrovascular accidents. Active chronic HCV infection is associated with an increased risk of ischemic heart disease[5]. Including the myocardium, the importance of HCV infection has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, and left ventricular (LV) diastolic dysfunction[6]. There are few reports about the possibility of RV dysfunction, in those patients[7,8]. Right ventricular functions have not been well studied in HCV patients and to date, no study shows a direct correlation between severity of HCV infection and level of impairment of right ventricular functions. The present study aimed to investigate the possibility of using myocardial deformation indices by two- (2D) and three-dimensional (3D) speckle tracking echocardiography as an early imaging biomarker of right ventricular (RV) function affection in HCV patients even in early stages without significant hepatic cirrhosis.

Methods

Study design

The study obtained ethical approval from the local research ethics committee, and written informed consent was obtained from patients before enrollment. The study included patients of both genders, above 18 years old with confirmed HCV infection proved by PCR test. Patients with poor echocardiographic images, valvular heart disease, arrhythmias, pericardial or ischemic heart diseases, hypertension, Diabetes mellitus, chronic kidney or lung disease, and obesity were excluded. Also, patients who had previously received anti-HCV treatment were excluded from the study. The study recruited 108 patients; and divided into two groups: group (A) included 54 HCV patients and Group (B) included 54 healthy subjects (controls) for whom an echocardiographic study was carried out according to the recommendation of the European Association of cardiovascular imaging & American society of echocardiography using (Philips Ultrasound field service company, EPIQ 7 Q lab version 10.8.5) machine.

Right ventricular function assessment

Right ventricular (RV) function assessment was done using conventional parameters including, the Right Ventricular Index of Myocardial Performance (RIMP) which is an index for global RV performance. It was assessed in the study by using tissue Doppler over the lateral tricuspid annulus. The cut-off value was 0.54 or more by TDI indicating RV dysfunction[9]. Tricuspid annular plane systolic excursion (TAPSE) was assessed as well. It represents a measure of RV longitudinal function. It was measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view. The cut-off value for TAPSE < 17 mm is highly suggestive of RV systolic dysfunction[9]. Fractional area change (FAC) is a measure of RV systolic function that has been shown to correlate with RV EF by magnetic resonance imaging (MRI). It's defined as (end-diastolic area - end-systolic area)/end-diastolic area x 100. FAC was obtained by tracing the RV endocardium both in systole and diastole from the annulus, along the free wall to the apex, and then back to the annulus, along the interventricular septum. RV FAC < 35% indicates RV systolic dysfunction[9,10]. Tricuspid Annular plane Systolic Velocity (S') was assessed using pulse-wave Doppler placed in the lateral annulus parallel to the free wall. It was vital to keep the basal segment, and the annulus aligned with the Doppler cursor to avoid velocity underestimation. An S' velocity less than 9.5 cm/sec measured on the free-wall side indicates RV systolic dysfunction[9,10]. Advanced RV function assessment performed using speckle tracking technique allowing better evaluation of the complex, crescent-shaped RV. Images were acquired in RV-focused view, and a frame rate of 70 to 80 frames/s, then the region of interest was obtained by tracing the RV endocardial borders at the level of the septum and the free wall in a still frame at end-systole. Global Longitudinal strain was attained from the mean of 3 RV free wall segments (the basal, mid, and apical segments of the RV free wall)[11]. Left ventricular (LV) systolic and diastolic functions were assessed by modified Simpson's and mitral inflow Doppler interrogation according to the guidelines for exclusion of LV impairment that might cause RV dysfunction(9).

Statistical analysis

The data was analyzed using the statistical package for the social sciences (version 24.0; SPSS Inc., Chicago, Illinois, USA) software for Windows. Continuous variables were expressed as mean ± SD and categorical variables were expressed as percentage. A P value less than or equal to 0.05 was considered statistically significant. Fisher's exact test and chi-square test were used for statistical analysis of categorical variables as appropriate. Due to the skewness of the data, means differences between investigated groups were assessed by the Mann-Whitney U test. Correlations analyses were performed using the Spearman correlation test. Logistic regression was performed for multivariable analysis for all univariate relevant variables that discriminate right ventricular dysfunction for hepatitis C patients. Discrimination of the logistic models was assessed by calculating the area under the receiver operating characteristic (ROC) curve.

Results

This comparative study included 54 hepatitis C patients and 54 healthy controls and aimed at assessing the detection of subclinical right ventricular dysfunction in patients with chronic HCV infection. Baseline characteristics for patients and controls are presented in (Table 1). There were no significant differences in characteristics between the two groups. Groups are well matched apart from a slightly but statistically significant rise in the LV filling pressure (LV E/E') in the HCV group. Details of the right ventricular echocardiographic parameters of both HCV patients and controls are shown in (Table 2). Conventional parameters are entirely in the normal range without significant differences between HCV and controls including RIMP, TAPSE, FAC, and S' velocity (P value: 0.41, 0.11, 0.74, and 0.11, respectively). Segmental strain showed that apical strain value was significantly lower in cases compared to controls (-19.19 ± -7.23 vs. -21.64 ± -2.07, p<0.001). Pulmonary artery pressure was also slightly higher but significant in cases compared to controls (15.81 ± 4.51 vs. 12.46 ± 3.32, p < 0.001). While Global longitudinal strain (-24.2 ± -4.91% vs. -24.98 ± -2.61%, p = 0.171) were comparable in both groups. Logistic regression analysis was used to assess predictors of right ventricular dysfunction among HCV patients (Table 3). As the apical strain value increases by one unit, the odds of having right ventricular dysfunction in HCV patients increase by 19.2% (p=0.005). The area under the curve (AUC) was 0.731(0.58 – 0.875) (p=0.004) as shown by Figure 1: ROC curve analysis of apical strain for prediction of right ventricular dysfunction (Figure 1). A value of -18.5 for apical strain was found to be the best cut-off point to predict RV dysfunction in HCV patients, with sensitivity = 70.97% and specificity = 65.22% (Table 4).

Table 1. Baseline characteristics of the studied sample (n= 108)

Variables	Total (n=108)	Hepatitis C		p-value
		Cases (n=54)	Controls (n=54)	
Age (years), mean ± SD	66.56 ± 7.66	69.39 ± 5.88	66.72 ± 8.22	0.086 [a]
Gender, n (%)				
Male	72 (66.7)	34 (63)	38 (70.4)	0.54 [b]
Female	36 (33.3)	20 (37)	16 (29.6)	
Smoking, n (%)				
Absent	94 (87.1)	46 (85.2)	48 (88.8)	0.56 [b]
Present	14 (12.9)	8 (14.8)	6 (11.1)	
BMI (kg/m^2)	25.42 ± 4.42	25.02 ± 3.93	25.81 ± 4.86	0.253 [a]
LV EF	63.9 ± 5.13	64.4 ± 6.1	63.4 ± 4.1	0.24 [a]
LV E/E'	9.3 ± 2.5	9.8 ± 2.8	8.7 ± 2.1	**0.043*** [a]

[a] *p-values are based on Mann Whitney U test. Statistical significance at P < 0.05*

[b] *p-values are based on Chi square test. Statistical significance at P < 0.05*

Table 2. Right ventricular echocardiographic parameters of HCV patients and controls group

Variables	**Total (n=108)** mean ± SD	Hepatitis C		p-value
		Cases (n=54) mean ± SD	**Controls (n=54)** mean ± SD	
RIMP	0.48 ± 0.04	0.48 ± 0.04	0.47 ± 0.04	0.419
TAPSE	21.41 ± 2.53	21.07 ± 2.79	21.74 ± 2.21	0.115
FAC	50.49 ± 6.88	50.7 ± 7.25	50.27 ± 6.55	0.74
S' velocity	13.11 ± 1.69	12.96 ± 2.11	13.25 ± 1.12	0.116
Basal strain	-27.98 ± -5.03	-28.05 ± -6.21	-27.91 ± -3.52	0.825
Mid strain	-25.25 ± -5	-25.09 ± -6.5	-25.4 ± -2.85	0.318
Apical strain	-20.41 ± -5.43	-19.19 ± -7.23	-21.64 ± -2.07	**<0.001***
GLS	-24.59 ± -3.93	-24.2 ± -4.91	-24.98 ± -2.61	0.171
PAP	14.14 ± 4.29	15.81 ± 4.51	12.46 ± 3.32	**<0.001***

[a] *p-values are based on Mann Whitney U test. Statistical significance at P < 0.05*

Discussion

In this study, we recruited 108 subjects; divided into two: group (A) included 54 HCV patients, and group (B) included 54 healthy subjects (controls). Both groups were cross-matched for age, gender, smoking, obesity, and LV function. Echocardiography was done for all individuals to assess the correlation between RV function and HCV infection. Regarding gender, our study has shown that HCV is more common among males as 63% were males while females formed 37% of the HCV patients, which is consistent with previous studies[12,13]. This is confirmed by Boghdady et al, whose study enrolled 1000 participants; they were randomly selected from different districts in Kafr El Sheikh Governorate, and it showed a 2.5:1 male predominance[13]. LV filling pressure was measured by the ratio between E and E' medial and results showed that HCV patients had significantly higher LV filling pressure than that of the controls (9.8 ± 2.8 vs 8.7 ± 2.1, P = 0.043). This is consistent with another study conducted and included 50 anti-HCV positive patients and 50 persons for control groups where LV parameters (including LV EF and diastolic dysfunction) were measured. In that study, the ratio of E/E' medial was found to be higher (7.6 ± 1.51 and 6.8 ± 1.72, P = 0.0001) with no other statistically significant difference found between the two groups regarding the left ventricle systolic and diastolic parameters[8].

Table 3. Logistic regression analysis of right ventricular dysfunction among HCV patients

Variables	β (SE)		OR (95% CI)	p-value
Constant	2.033	1.561	-	0.19
Apical strain	0.176	0.063	1.192 (1.05 – 1.34)	**0.005***
PAP	0.104	0.077	1.110 (0.955 – 1.29)	0.174

** Statistical significance < 0.05.*

Table 4. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy at different cut-off levels of apical strain for prediction of right ventricular dysfunction among HCV patients

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	accuracy
-18.25	67.74%	65.22%	72.41	60%	66.7%
-18.5	70.97%	65.22%	73.33%	62.5%	**68.52%**
-19	70.97%	60.78%	70.97%	60.87%	66.7%

** PPV, positive predictive value; NPV, negative predictive value.*

Regarding the effect of chronic hepatitis C virus (HCV) infection on the right ventricular (RV) function and pulmonary hypertension, there is little data about this concern in the literature. Only a similar study was conducted in 2014 that showed that there is a possible relationship between HCV infection and RV dysfunction[8]. Demir et al, in that study, enrolled two groups the first group contained 50 patients with anti-HCV antibodies, normal liver enzymes, and hadn't received any antiviral treatment, while the other control group consisted of 50 subjects who did not have any structural cardiac pathologies. In HCV positive group, the RV FAC, TAPSE, and S' velocity 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); RIMP, was found to be higher in patients groups than control (0.47 ± 0.7 vs 0.33 ± 0.2, P < 0.001)[8]. Dalbeni et al, in their study that assessed left and right ventricular function in 65 HCV patients with mild liver fibrosis and 60 (age, sex, BMI, and cardiovascular risk factors) matched controls, showed that TAPSE in the HCV group was 14.8 ±6.1 mm (mean ± SD) vs TAPSE controls 18.9±1.9 mm (p<0.001) and this dysfunction was not related to the viral load measured by PCR[14]. However; this was contradicted in our study as there was no statistically significant difference between cases and control groups in the following parameters: TAPSE (21.07 ± 2.79 vs. 21.74 ± 2.21), RV-FAC (50.7 ± 7.25 vs. 50.27 ± 6.55), S' velocity (12.96 ± 2.11 vs. 13.25 ± 1.12), RIMP (0.48 ± 0.04 vs. 0.47 ± 0.04) or global longitudinal strain (-24.2 ± -4.91 vs. -24.98 ± -2.61)[14]. Two parameters showed statistically significant differences between cases and control groups. First, the systolic pulmonary artery pressure (SPAP) (15.81 ± 4.51 vs 12.46 ± 3.32, $P < 0.001$) however was within the normal range. This is consistent with what was described by Demir et al, where the SPAP was found to be higher in HCV cases (36.3 ± 9.9) vs the control group (23.1 ± 8 mmHg, $P < 0.001$)[8]. Our study only included patients with child (A) classification, with no patients with advanced liver cirrhosis included. However, the effect of liver cirrhosis was discussed in the literature, whereas in a study conducted in Patients with Hepatitis C-related Cirrhosis, 481 patients were identified with hepatitis C-related cirrhosis. None of those patients had documented interstitial lung disease, acute pulmonary embolism, chronic thromboembolic disease, or a positive anti-neutrophil cytoplasmic antibody.

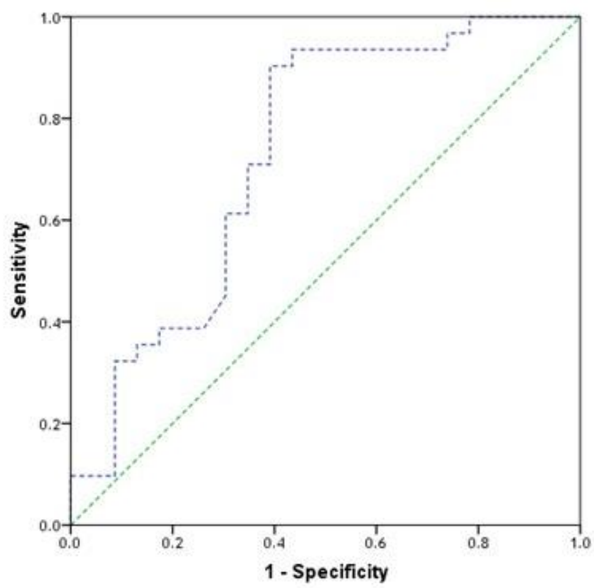

Figure 1: ROC curve analysis of apical strain for prediction of right ventricular dysfunction

The prevalence of pulmonary HTN in patients with hepatitis C-related cirrhosis was 28% (134/481 patients)[15]. Second, the apical longitudinal strain values were lower in the case groups in comparison to controls (-19.19 ± -7.23 vs -21.64 ± -2.07, $P < 0.001$). There was no data in the literature about RV regional strain in HCV patients. This peculiar regional strain pattern has not been described before in literature but might be pathognomonic for cardiac involvement in chronic HCV patients. Logistic regression analysis showed that apical longitudinal strain is a predictor of right ventricular dysfunction among HCV patients with the best cut-off value: of -18.5 having a sensitivity of 70.97%, specificity of 65.22%, and accuracy of 68.52%. Thus, the RV apical longitudinal strain seems a promising parameter to identify subclinical RV myocardial impairment in HCV patients.

Study Limitations

This study is limited by the small sample size of patients included in this study.

Patients were selected only from a single center. Therefore, large-scale, multi-centered studies must confirm the present findings. These results can't be applied to HCV patients experiencing co-morbidities.

Conclusion

Speckle tracking has been proven to detect early myocardial affection in chemotherapy-treated patients. In this study, speckle tracking namely RV segmental apical longitudinal strain proved its ability to detect subclinical RV dysfunction in HCV patients even with normal baseline conventional parameters, however, further studies in this area are still recommended on a large number of patients.

Conflict of interest

The authors declared that there are no conflicts of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Blach S, Zeuzem S, Manns M, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet Gastro Hep 23. 2017;2(3):161-76.
2. Elgharably A, Gomaa AI, Crossey MM, et al. Hepatitis C in Egypt–past, present, and future. Int J Gen Med 2017;10: 1-6.
3. Gomaa A, Allam N, Elsharkway A, et al. Hepatitis C infection in Egypt: prevalence, impact and management strategies. Hepat Med. 2017; 9:17.
4. Cacoub P, Comarmond C, Domont F, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. Ther Adv Infec Dis. 2016;3(1):3-14.
5. Domont F, Cacoub PJLI. Chronic hepatitis C virus infection, a new cardiovascular risk factor? Liver Int. 2016;36(5):621-7.
6. Raedle-Hurst TM, Welsch C, Forestier N, et al. Validity of N-terminal propeptide of the brain natriuretic peptide in predicting left ventricular diastolic dysfunction diagnosed by tissue Doppler imaging in patients with chronic liver disease. Eur J Gastroenterol Hepatol. 2008;20(9):865-73.
7. Demir M, Demir CJSmj. Effect of hepatitis C virus infection on the left ventricular systolic and diastolic functions. South Med J. 2011;104(8):543-6.
8. Demir C, Demir MJIjoc. Effect of hepatitis C virus infection on the right ventricular functions, pulmonary artery pressure and pulmonary vascular resistance. Int J Clin Exp Med. 2014;7(8):2314.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovas Imaging. 2015;16(3):233-71.
10. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7):685-713
11. Toyoda T, Baba H, Akasaka T, et al. Assessment of regional myocardial strain by a novel automated tracking

system from digital image files. J Am Soc Echocardiogr. 2004;17(12):1234-8.
12. Niu Z, Zhang P, Tong YJS. Age and gender distribution of Hepatitis C virus prevalence and genotypes of individuals of physical examination in WuHan, Central China. Springerplus. 2016;5(1):1557.
13. Boghdady IM, ElKafrawy NAE, Shoaib AAEM, et al. Seroprevalence and risk factors of hepatitis C virus infection among population in Kafr El Sheikh Governorate. Menoufia Med J. 2014;27(4):686.
14. Dalbeni A, Romano S, Imbalzano E, et al. The wrong or "right" effects of HCV on cardiac function in patients with low-mild liver fibrosis: A case-control study. J. Hepatol. 2018;68:S408.
15. Salyers WJ, Christman E, Seecheran NA, et al. Prevalence of Pulmonary Hypertension in Patients With Hepatitis C-Related Cirrhosis at a Non-Liver Transplant Center. Gastroenterology. 2011;140(5):S-958-S-9.