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Right ventricular dysfunction in cirrhosis: A speckle-tracking echocardiography study

Sirozda sağ ventrikül disfonksiyonu: Speckle-tracking ekokardiyografi çalışması

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Abstract

Aim: The majority of studies on cardiac dysfunction in patients with cirrhosis are associated with left ventricular (LV) myocardial dysfunction, with fewer studies on right ventricular (RV) function. The aims of this study were to evaluate biventricular function, particularly RV function, in patients with cirrhosis and investigate its relationship with disease severity.

Methods: We included 50 hospitalized and ambulatory patients with cirrhosis and 33 healthy controls. Echocardiographic evaluation was performed with speckle-tracking analysis. Liver disease was graded according to Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.

Results: In our study, the most prevalent etiology of cirrhosis was viral hepatitis (60%), followed by non-alcoholic fatty liver disease (24%). RV-global longitudinal strain (GLS) and LV ejection fraction (EF) values were lower in patients with cirrhosis compared to the control group (both, P=0.001). LVEF was <55% in 19 (38%) patients. Decreases in RV-GLS and LVEF values were more common in patients with ascites (both, P=0.001). However, measurements of RV-GLS and LVEF did not distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores. LV-GLS values between patients with cirrhosis and the control group were similar (P=0.896).

Conclusions: This study showed that RV function was impaired in patients with cirrhosis and more commonly, in patients with ascites. However, values of RV-GLS did not distinguish the degree of severity of liver disease. In addition, the LVEF was low and LV-GLS was normal in patients with cirrhosis.

Keywords: Cirrhotic cardiomyopathy, Right ventricular dysfunction, Echocardiography, Speckle-tracking analysis

Öz

Amaç: Sirozlu hastalarda kardiyak disfonksiyon üzerine yapılan çalışmaların çoğu, sol ventriküler (LV) miyokardiyal disfonksiyon ile ilişkilidir ve sağ ventrikül (RV) fonksiyonu üzerine daha az çalışma vardır. Bu çalışmanın amacı sirozlu hastalarda özellikle RV fonksiyonu olmak üzere, biventriküler fonksiyonu değerlendirmek ve hastalık şiddeti ile ilişkisini araştırmaktır.

Yöntemler: Hastanede yatan ve ayakta tedavi gören 50 siroz hastası ve 33 sağlıklı kontrol çalışmamıza dahil edildi. Ekokardiyografik değerlendirme speckle-tracking analizi ile yapıldı. Karaciğer hastalığı Child-Pugh ve Son Evre Karaciğer Hastalığı Modeli (MELD) puanlarına göre derecelendirildi.

Bulgular: Çalışmamızda sirozun en yaygın etiyolojisi viral hepatit (%60), ardından non-alkolik yağlı karaciğer hastalığı (%24) idi. Sirozlu hastalarda RV-global longitudinal strain (GLS) ve LV ejeksiyon fraksiyonu (EF) değerleri kontrol grubuna göre daha düşüktü (her ikisi de P=0.001). LVEF, 19 (% 38) hastada < %55 idi. Asitli hastalarda RV-GLS ve LVEF değerlerindeki düşüşler daha sıktı (her ikisi de, P=0,001). Bununla birlikte, RV-GLS ve LVEF ölçümleri, Child-Pugh ve MELD skorlarına göre karaciğer hastalığının şiddet derecesini ayırt etmedi. Sirozlu hastalar ile kontrol grubu arasındaki LV-GLS değerleri benzerdi (P=0.896).

Sonuç: Bu çalışma, RV fonksiyonunun sirozlu hastalarda ve daha sık olarak asitli hastalarda bozulduğunu göstermiştir. Bununla birlikte, RV-GLS değerleri, karaciğer hastalığının şiddet derecesini ayırt etmedi. Ayrıca sirozlu hastalarda LVEF düşüktü ve LV-GLS normaldi.

Anahtar kelimeler: Sirotik kardiyomiyopati, Sağ ventrikül disfonksiyonu, Ekokardiyografi, Speckle-tracking analizi

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Introduction

The presence of myocardial dysfunction in patients with liver cirrhosis has been defined since the 1960s, and many different cardiac abnormalities associated with liver cirrhosis are grouped under the term cirrhotic cardiomyopathy (CCM) [1]. Components in CCM include impaired cardiac contractility with systolic dysfunction, diastolic dysfunction, a long Q-T interval, and other electromechanical abnormalities [2]. Advanced cirrhosis is associated with a hyperdynamic circulation characterized by high cardiac output and increased cardiac effort, but this may be clinically latent due to a reduced afterload (reduced systemic vascular resistance) and may occur with physical or pharmacological strain [3,4]. In CCM, left ventricular (LV) end-diastolic pressure increases after exercise. However, there is no expected increase in the LV ejection fraction (LVEF) due to an inadequate response in terms of elevation of the cardiac reserve [5].

In cirrhotic patients, most studies have focused on LV function, which is generally examined with tissue Doppler echocardiography [6]. However, cardiac dysfunction is usually underdiagnosed, or diagnosed only when overt cardiac failure has developed in these patients [7]. In cirrhotic patients, right ventricular (RV) dysfunction is associated with prognosis, and a large number of cirrhotic patients exhibit symptoms of RV dysfunction [8]. Therefore, it is extremely important to determine RV as well as LV function in cirrhotic patients [7,9].

Recently, speckle-tracking strain examination has been suggested as a sensitive and proper method for evaluating subclinical systolic dysfunction in several diseases [10]. Speckle-tracking echocardiography delivers objective quantitative measurements of LV and RV (biventricular) segmental and global function without being affected by ventricle size and is useful for evaluating cardiac remodeling [9].

This study compared biventricular function, particularly RV function, between patients with cirrhosis and healthy controls using novel echocardiographic techniques and also investigated whether cardiac abnormalities are associated with the severity and etiology of the disease.

Materials and methods

Fifty consecutive cirrhotic patients who were hospitalized or followed as outpatients and 33 sex- and age-matched healthy subjects were included in this prospective study. The diagnosis of cirrhosis was established by a combination of clinical, biochemical, ultrasonographic, and/or histological findings. Patients with a known history of hypertension, cardiac disease, relevant electrocardiogram abnormalities, malignancy, or active infection were excluded from the study. A detailed medical history, including the etiology and duration of liver disease, was obtained from all subjects. The presence or absence of ascites, esophageal varices, and hepatic encephalopathy was recorded. The presence or absence of ascites was confirmed by ultrasound before enrollment. Patients without ascites were named pre-ascites cirrhotic patients. For laboratory evaluation, liver enzymes, serum bilirubin, albumin level, activated partial thromboplastin time, prothrombin time, the international normalized ratio (INR), and serum creatinine level were measured. Liver function was assessed using Child-Pugh, Model for End-Stage Liver Disease (MELD), and MELD-Sodium (MELD-Na) scores [11,12]. Patients were divided into three prognostic groups according to their Child-Pugh scores (groups A, B, and C). In addition, patients were grouped according to their MELD ($\geq$ 15 and $<$ 15) and MELD-Na ($\geq$ 20 and $<$ 20) scores, as described in a previous study [13].

The study protocol was approved by the ethics committee of our hospital (Approval number: 19.02.2020/41) and conformed to the Declaration of Helsinki. All included patients provided informed consent.

Echocardiography

In this study transthoracic echocardiography was performed by the same cardiologist using the Vivid S60 (GE Vingmed Ultrasound, Horten, Norway) echocardiography system with an M5S (2-4 MHz) probe. The standard apical four- and two-chamber and parasternal axis images were obtained via conventional 2D gray-scale and conventional Doppler echocardiography according to the recent recommendations of the American Society of Echocardiography (ASE) [14]. RV parameters were also examined according to the guidelines of ASE. The modified Simpson's method was used with the 2D echocardiographic technique to measure LVEF [15]. This method also recommended by ASE and it accomplishes by monitoring the LV border in the apical four- and two-chamber images in both end-systole and diastole.

Speckle-tracking echocardiography analyses

Speckle-tracking analysis was performed using the EchoPAC system (GE Healthcare, Chicago, IL, USA). Considering the recommendations of EACVI / ASE / Industry Task Force consensus [16], the endocardial border was manually monitored in the end-systolic frame, starting from one end of the mitral annulus and ending at the other. Apical two-chamber and four-chamber grayscale images were stored digitally for analysis. The strain values of all segments were recorded and averaged to find the LV-GLS and strain ratio. Radial strain curves, epicardial, and endocardial circumferential strain curves were analyzed by the software in the short axis images. For RV GLS, RV strain was analyzed in four segments, three of the right ventricular free wall (basal, middle, and apical segment) and one part of the ventricular septum. We used global strain for RV. LV and RV strain values were analyzed by repeated measurements at two different times by the same cardiologist.

Statistical analysis

The normality of the distributions of the numerical variables were tested with the Shapiro-Wilk test. Student's t-test was used for analyzing statistically significant difference between two normally distributed variables in different groups, and the Mann-Whitney U test was used to compare non-normally distributed variables between the two groups. In comparisons of three or more independent groups, the analysis of variance test was used for normally distributed groups and the Kruskal-Wallis test was used for non-normally distributed groups. Linear regression analysis was performed to investigate the influence of each variable on the measurements. SPSS 22.0 software for Windows (IBM Corp.) was used for the analyses. A *P*-value <0.05 denoted significance.

Results

This study included 50 (62% males) cirrhotic patients and 33 (51.5% males) healthy volunteers. The median age of the patients was 57 years (range: 46–67 years), and that of the control group was 55 years (range: 45.5–66 years). The most prevalent etiology of cirrhosis was viral hepatitis (60%), followed by non-alcoholic fatty liver disease (24%). LVEF, LV global longitudinal strain (LV-GLS), and RV global longitudinal strain (RV-GLS) measurements were similar among patients according to cirrhosis etiology (P>0.05). Patients were classified into groups A (19 patients), B (14 patients), and C (17 patients) according to disease severity on the basis of the Child-Pugh score. MELD scores of 25 (50%) cirrhotic patients were < 15 (Table 1). Cirrhosis was decompensated in 31 (62%) patients, with mean Child-Pugh and MELD scores of 7.50 (3.22) and 15.84 (7.92), respectively, at admission. Of the 50 patients, 18 had no history of ascites. The remaining 32 patients had obvious ascites clinically, which was confirmed on ultrasound. There was a significant relationship between the presence of ascites and RV-GLS and LVEF measurements (both, P=0.001), but not with LV-GLS measurements (P=0.307).

Table 1: Demographic, clinical, and laboratory characteristics of the patients

	Patients (n=50)
Age, mean (SD)	56.96 (13.33)
Male sex, n (%)	31 (62%)
Cirrhosis etiology, n (%)	
Viral	30 (60%)
NAFLD	12 (24%)
Alcohol	4 (8%)
Other	4 (8%)
Child-Pugh class, n (%)	
Group A	19 (38%)
Group B	14 (28%)
Group C	17 (34%)
MELD score, mean (SD)	15.84 (7.92)
MELD-Na score, mean (SD)	16.88 (8.35)
Esophageal varices present, n (%)	
Grade I	16 (32%)
Grade II	12 (24%)
Grade III	17 (34%)
Esophageal variceal bleeding, n (%)	7 (14%)

IQR: interquartile range, NAFLD: non-alcoholic fatty liver disease, MELD: Model for End-Stage Liver Disease, MELD-Na: Sodium Model for End-Stage Liver Disease, SD: standard deviation

RV-GLS measurements in cirrhotic patients were significantly lower than those in the control group (P=0.001). However, no relationship was found between the Child-Pugh (P=0.191), MELD (P=0.331), and MELD-Na (P=0.907) groups and RV-GLS.

LV-GLS measurements were lower in females than in males (P=0.003), but they were similar between the patient and control groups (P=0.896) and among Child-Pugh groups (P=0.516). In addition, LV-GLS measurements did not differ between MELD or MELD-Na groups (P=0.516 and P=0.775, respectively).

LVEF measurements were significantly lower in the patients than in the controls (P=0.001). There was no difference in LVEF measurements based on sex (P=0.085), MELD score (P=0.613), or MELD-Na score (P=0.583). Nineteen patients (38%) had an LVEF < 55%. The majority of patients with LVEF < 55% were classified as Child-Pugh B or C. Of the patients with LVEF < 55%, based on Child-Pugh score, nine (47.4%) were in group C, seven (36.8%) in group B, and three (15.8%) were in group A (P=0.04). There were no significant differences among the groups in terms of mean LVEF values (P=0.188). Also, there was a statistically significant relationship between LVEF and LV-GLS (P=0.001) (Table 2).

There were no significant relationships between LV-GLS, LVEF, and RV-GLS measurements and the presence of esophageal varices, encephalopathy, thrombocytopenia, and increased INR (P<0.05).

Table 2: Relationship between echocardiographic measurements and various parameters

	LV-GLS	RV-GLS	LVEF
Sex			
Males (n=48)	20.12 (2.87) *	18.81 (3.73)	63.13 (12.31)
Females (n=35)	18.52 (1.94)	19.88 (4.05)	62.66 (11.46)
Groups			
Cirrhotic patients (n=50)	19.42 (2.83)	17.05 (3.49) **	55.94 (9.65) **
Control group (n=33)	19.49 (2.33)	22.61 (0.93)	73.52 (5.26)
Child-Pugh class			
Group A (n=19)	19.96 (2.65)	18.03 (3.18)	59.11 (8.60)
Group B (n=14)	18.82 (2.67)	15.79 (3.76)	53.50 (9.66)
Group C (n=17)	19.29 (3.18)	17.01 (3.44)	54.41 (10.33)
MELD score			
< 15 (n=25)	19.03 (2.62)	17.54 (3.44)	56.64 (9.26)
≥ 15 (n=25)	19.53 (3.07)	16.57 (3.54)	55.24 (10.17)
MELD-Na score			
< 20 (n=33)	19.42 (2.71)	17.09 (3.53)	56.48 (9.43)
≥ 20 (n=17)	19.42 (3.12)	16.97 (3.52)	54.88 (10.28)
Ascites			
Pre-ascites (n=18)	19.97 (2.59)	18.18 (3.22)	58.89 (8.56)
Ascites (n=32)	19.11 (2.95)	16.42 (3.52) **	54.28 (9.96) **
Esophageal varices			
Absent or Grade I (n=21)	18.95 (2.73)	18.86 (3.45)	54.62 (9.08)
Grade II or III (n=29)	19.75 (2.89)	17.18 (3.56)	56.89 (10.09)
Cirrhosis etiology			
Hepatitis (n=30)	19.84 (2.81)	16.91 (3.35)	57.50 (9.96)
NAFLD (n=12)	17.92 (2.06)	16.76 (3.82)	51.75 (7.16)
Alcoholic (n=4)	19.25 (3.73)	17.60 (3.62)	54.50 (12.34)
Other (n=4)	20.93 (3.31)	18.45 (4.51)	58.25 (10.90)

All numbers are presented as the mean (SD), LV-GLS: left ventricle global longitudinal strain, RV-GLS: right ventricle global longitudinal strain, LVEF: left ventricle ejection fraction, NAFLD: non-alcoholic fatty liver disease, MELD: Model for End-Stage Liver Disease; MELD-Na: Sodium Model for End-Stage Liver Disease, * P=0.003, males vs. females, ** P=0.001, cirrhotic patients vs. control group, and pre-ascites vs. ascites

Discussion

In this study, we used speckle-tracking strain analysis for cardiac evaluation in patients with cirrhosis of different etiologies. We showed that the RV-GLS and LVEF were decreased in cirrhotic patients. In addition, we found a relationship between RV-GLS and the presence of ascites in cirrhotic patients, with RV-GLS values lower in patients with ascites. However, measurements of RV-GLS did not distinguish the degree of severity of liver disease on the basis of the Child-Pugh and MELD scores. In addition, our study results showed that patients with cirrhosis have normal LV-GLS.

In recent years, studies have focused on the presence of specific cardiac abnormalities in cirrhotic patients [6,17]. Cardiovascular complications in cirrhosis may occur due to humoral, nervous, and hemodynamic changes. The CCM criteria established at the World Gastroenterology Congress in 2005 include echocardiographic parameters for defining subclinical cardiac dysfunction without obvious structural abnormalities [3]. However, the CCM Consortium has recently proposed new criteria based on novel cardiovascular imaging parameters [4]. CCM indicates systolic and diastolic dysfunction and electrophysiological abnormalities [18]. In the 2005 criteria for CCM, LV dysfunction is defined by a low resting LVEF (< 55%) and/or the presence of a blunted contractile response in a myocardial stress test (LVEF stress test >5%). However, due to limited assessment of impaired contractile responses to stress testing in cirrhotic patients, the CCM Consortium recommended evaluation of GLS (normal value –18% to –22%) to detect LV systolic function in patients with cirrhosis with a preserved LVEF (normal value > 50%). In addition, the CCM Consortium

recommendations include minimum criteria for the diagnosis of advanced diastolic dysfunction in cirrhotic patients without known heart disease [4].

The prognostic value of RV function in cardiovascular disease have been shown in several studies [8]. Therefore, it has become increasingly important to quantify RV systolic function. In cirrhotic patients, impaired liver function contributes to increased preload in the right heart. High hepatic venous pressures causing increased preload can deteriorate RV functions. RV function is more difficult to evaluate than LV function. The fine changes in the systolic and the diastolic functions of the heart, which can be seen in cirrhotic patients, may not be detected with the conventional transthoracic echocardiography [19]. Novel echocardiographic techniques can improve the quantitative assessment of RV function. Speckle-tracking strain analysis is a sensitive and reliable method that can accurately evaluate RV and LV function in patients with cirrhosis. This method enables the detection of ventricular dysfunction in three directions—longitudinal, circumferential, and radial, without being affected by ventricle size. Longitudinal deformation is a reliable measure of the extent of myocardial damage, manifests early, and suggests subendocardial disease. Circumferential deformation indicates transmural damage and it manifests relatively late in the disease course [20]. In our study, using speckle-tracking strain analysis, we showed that RV-GLS measurements were significantly lower in patients with cirrhosis than in controls. Our results are similar to those of other studies that found reduced RV strain in patients with cirrhosis [19,21]. In addition, in our study, RV-GLS measurements were lower in patients with ascites than in patients without. Our study showed the importance of evaluating RV function in patients with cirrhosis. However, the RV-GLS measurements were not able to distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores.

We found that LV-GLS values were normal in patients with cirrhosis. In addition, there were no differences in LV-GLS values in patients with cirrhosis according to disease severity and etiology. Sampaio et al. [6] reported lower LV-GLS in patients with cirrhosis compared to the control group, but did not find significant differences in terms of LV-GLS between cirrhotic patient groups according to Child-Pugh scores and etiology. A recent study evaluated LV-GLS in cirrhotic patients and found no differences between patients with and without ascites [22]. Similarly, we could not find a significant difference in LV-GLS measurements between patients with and without ascites in our study.

The EF is the most widely used parameter for representing global LV systolic function. In CCM, the systolic function is usually normal at rest, but the expected increases in LVEF after exercise are absent or insufficient, indicating an inadequate response of the ventricular reserve to an increase in ventricular filling pressure. In our study, we found a lower LVEF in cirrhotic patients compared to control patients. However, the LVEF has been reported to be normal in some studies [23,24], increased in some studies [25,26], and decreased in others [27,28]. A resting EF < 55% has been suggested as a diagnostic criterion for systolic dysfunction in patients with cirrhosis. However, EF is highly dependent on loading conditions, and a higher threshold value may be needed for patients with cirrhosis due to peripheral vasodilation and reduced afterload [29]. The EF is not only an index of contractility but also a subject to both heart rate and valvular function [30]. These reasons probably explain the variable resting EF findings in studies of cirrhotic patients. In addition, the LVEF was lower in patients with ascites in our study. Similarly, in a study by Pozzi et al. [27], the LVEF was reported to be decreased in patients with ascites.

Limitations

The limitations of this study were the small study group and the lack of inclusion of a stress test (physical activity or pharmacological stress) that could better prove subclinical cardiac dysfunction. Also, diastolic dysfunction and dilation of both left and right ventricles require evaluation with additional studies.

Conclusions

This study showed that RV function was impaired in patients with cirrhosis and this was more common in patients with ascites. Patients with cirrhosis exhibited significantly decreased RV function compared with healthy controls. Speckle-tracking strain analysis can better detect subclinical RV dysfunction compared to normal traditional echocardiographic indices. However, the RV-GLS values did not distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores. We also showed that in cirrhotic patients, the LVEF was lower, but LV-GLS was similar between patients and controls. However, more studies are needed to determine the clinical significance of these findings.

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