ORIGINAL ARTICLE

Subclinical myocardial dysfunction in liver transplant candidates determined by using speckle tracking imaging

Karaciğer transplantasyonu adaylarında benek takibi görüntüleme ile belirlenen subklinik miyokart disfonksiyonu

⑤ Saadet Demirtaş İnci, M.D.,¹ ⑥ Leyla Elif Sade, M.D.,² ⑥ Cihan Altın, M.D.,² ⑥ Bahar Pirat, M.D.,² ⑥ Hilal Erken Pamukcu, M.D.,¹ ⑥ Sabiye Yılmaz, M.D.,³ ⑥ Haldun Müderrisoğlu, M.D.²

¹Department of Cardiology, Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey ²Department of Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey

³Department of Cardiology, Ministry of Health Sakarya University Training and Research Hospital, Sakarya, Turkey

ABSTRACT

Objective: There are various cardiovascular abnormalities in end-stage liver disease (ESLD). In these patients, left ventricular (LV) systolic function is normal at rest but deteriorates during stress. This deterioration may be due to subclinical myocardial dysfunction. This study evaluated global LV and right ventricular (RV) functions using 2-dimensional (2D) speckle tracking in patients with ESLD.

Methods: Forty liver transplant candidates with ESLD and 26 healthy individuals were included in the study. All of the patients underwent conventional echocardiographic measurements. Longitudinal, circumferential, and radial strain measurements, as well as apical and parasternal short-axis image recordings were obtained. All 2D strain measurements were performed with offline analysis using velocity vector imaging (VVI) software.

Results: In the apical 4- and 2-chamber measurements, the LV mean longitudinal strain was significantly lower in patients with ESLD compared with that of the control group (-16.0±3.2% versus -17.6±2.2%, -16.7±3.3% versus -18.7±2.1%; p=0.002, respectively). The LV mean circumferential strain did not differ between groups. The LV mean radial strain and RV longitudinal strain were significantly lower in patients with ESLD (45.4±10.7 vs. 52.7±10.8%; p=0.01 and -19.2±3.5% versus -21.5±3.6%; p=0.03, respectively).

Conclusion: Subclinical impairment of global LV and RV systolic functions were determined in liver transplantation candidates by using VVI. This deterioration was detected in longitudinal and radial deformation rather than circumferential deformation mechanics, which was consistent with early-stage LV myocardial dysfunction.

ÖZET

Amaç: Son dönem karaciğer hastalarında (SDKH) çeşitli kardiyovasküler anormallikler olduğu bilinmektedir. Bu hastalarda istirahatte sol ventrikül (LV) sistolik fonksiyonu normal saptanmasına karşın stres sırasında bozulmaktadır. Bu bozulma subklinik miyokardiyal işlev bozukluğundan kaynaklanıyor olabilir. Bu nedenle, bu çalışmada SDKH'da global LV ve sağ ventrikül (RV) fonksiyonlarını 2 boyutlu (2B) benek takibi görüntüleme yöntemi ile değerlendirmesi amaçlandı.

Yöntemler: Karaciğer nakil adayı olan 40 SDKH ile 26 sağlıklı birey çalışmaya dahil edildi. Tüm hastaların standart ekokardiyografik ölçümleri yapıldı. Uzunlamasına, sirkümferansiyel ve radyal strain ölçümleri için apikal ve parasternal kısa eksen görüntü kayıtları alındı. Tüm 2B strain ölçümleri alınan kayıtlardan, çevrim dışı analiz ile hız vektör görüntüleme (VVI) yazılım paketi kullanılarak ölçüldü.

Bulgular: Apikal 4- ve 2- boşluk ölçümlerde, LV ortalama uzunlamasına strain değeri, hasta grubunda kontrol grubuna göre anlamlı olarak daha düşüktü (-16.0±%3.2 ve -17.6±%2.2, p=0.03 ve -16.2±%3.3 ve -18.7±%2.1, p=0.002). LV ortalama sirkumferansiyel strain değerlerinde gruplar arasında fark saptanmazken, LV ortalama radyal strain ve RV uzunlamasına strain değerleri hasta grubunda anlamlı derecede daha düşük saptandı (45.4±10.7 ve %52.7±10.8, p=0.01 ve -19.2±%3.5 ve -21.5±%3.6, p=0.03).

Sonuç: Karaciğer nakil adaylarında, VVI yöntemi ile global LV ve RV sistolik fonksiyonlarında subklinik bozulma tespit edildi. Bu bozulma, LV'de miyokart hasarının erken evrede olmasıyla tutarlı olan sirkumferansiyel deformasyon mekaniğinden ziyade uzunlamasına ve radyal deformasyonda saptandı.

nation at the analysis of the state of the s **I** known to also experience cardiac abnormalities. ESLD causes cirrhotic cardiomyopathy (CCM), which is defined as chronic cardiac dysfunction in the absence of known heart disease in patients with cirrhosis, regardless of the etiology of the cirrhosis. [1] The specific diagnostic criteria for CCM include increased cardiac output due to peripheral vasodilatation, low systolic blood pressure, systolic and/or diastolic dysfunction, electrophysiological abnormalities, and chronotropic failure. [2] Overt heart failure is not common in CCM, though the prevalence is not known precisely since cardiac symptoms are not evident at rest. The cardiac response to stress is decreased, but stroke volume and contractile indices are typically normal or even increased at rest. However, under conditions of stress such as exercise, hemorrhage, or liver transplantation, cardiac function is impaired.[3] The pathogenesis includes deterioration of beta receptor functions, changes in transmembrane flow, and overproduction of cardiodepressant cytokines, such as nitric oxide.[4,5]

Speckle-tracking imaging (STI) enables quantification of deformation in longitudinal, radial, and circumferential directions and is more sensitive than conventional echocardiography in detecting subclinical ventricular dysfunction. The aim of this study was to evaluate left ventricular (LV) and right ventricular (RV) mechanical functions in liver transplant candidates using velocity vector imaging (VVI).

METHODS

Study population

Forty liver transplant candidates with ESLD and 26 age- and gender-matched healthy subjects were studied after obtaining informed consent from each patient. In total, 70 subjects were initially screened for study and 4 were not be included due to inadequate echocardiographic images. Hepatic cirrhosis was diagnosed by either liver biopsy or laboratory, clinical, and ultrasonography findings. Approval for this study was received from the Başkent University Clinical Research Ethics Committee (KA08/145).

Demographic and clinical characteristics, including age, sex, the presence of diabetes mellitus, hypertension, smoking, or dyslipidemia, and the results of the Child-Turcotte-Pugh Score for cirrhosis were noted.

Patients with coronary artery disease (CAD), systolic dysfunction, diabetes mellitus, hypertension, a cardiac rhythm other than sinus, valvular heart heart valve surgery, cardiomyhypertrophic opathy, renal dysfunction, chronic obstructive pulmonary disease, hepatopulmonary syndrome and pulmonary hypertension, sepsis, peripheral artery

Abbrev	Abbreviations:		
2D	Two-dimensional		
Aa	Late diastolic velocity		
CAD	Coronary artery disease		
CCM	Cirrhotic cardiomyopathy		
cTDI	Color-coded TDI		
Ea	Early diastolic color-coded		
	tissue velocities		
EF	Ejection fraction		
ESLD	End-stage liver disease		
LV	Left ventricular		
MPI	Myocardial performance		
	index		
RV	Right ventricular		
Sa	Peak systolic velocity		
STI	Speckle-tracking imaging		
TDI	Tissue Doppler imaging		

arterial disease, or poor echocardiographic image quality were excluded. CAD was defined as the presence of any of the following: (I) typical angina; (II) ischemic ST-T wave changes, pathological Q waves, or left bundle-branch block on ECG; (III) regional wall motion abnormalities on echocardiography; (IV) ischemia or any perfusion abnormality in stress imaging; or (V) history of myocardial infarction or coronary artery stenosis ≥50% detected with coronary angiography or a history of revascularization. Patients were defined as hypertensive if they had a diastolic pressure >90 mmHg or a systolic pressure >140 mmHg or if they were being treated with antihypertensive medication. An ejection fraction (EF) of <50% was accepted as LV systolic dysfunction.

Data acquisition and analysis

Echocardiography

Echocardiography was performed using an Acuson Sequoia C256 ultrasound system (Siemens Healthineers AG, Erlangen, Germany) equipped with a 3V2c broadband transducer. Two-dimensional (2D), Mmode, color and spectral Doppler measurements were analyzed by an experienced echocardiography specialist who was blinded to the patient's clinical data. Conventional 2D and Doppler echocardiography were performed according to the American Society of Echocardiography/European Association of Echocardiography recommendations. [6] LV end-diastolic volume, end-systolic volume, and EF were determined according to Simpson's modified biplane model. Tissue Doppler imaging (TDI) and color-coded TDI (cTDI) were performed from the apical 4-chamber view using pulsed-wave Doppler with a 3-mm sample volume at the mitral and tricuspid annular sites. Peak 640 Turk Kardiyol Dern Ars

systolic (Sa), early (Ea) and late (Aa) diastolic color-coded tissue velocities obtained from both annular sites were averaged (Fig. 1). The RV myocardial performance index (MPI) was calculated using the TDI of the tricuspid annulus.

Analysis of velocity vector imaging

A Siemens Syngo Workplace with VVI software (Siemens Healthineers AG, Erlangen, Germany) was used to perform 2D-STI. Digital cineloops from the apical 4- and 2-chamber view and parasternal short--axis view were obtained at a frame rate of 50-90 frames/second from the peak of the R wave and stored on optical disks in the Digital Imaging and Communications in Medicine format for offline analysis. All of the analyses were performed by a single operator who was blinded to all clinical data. Echocardiographic cineloops were obtained by recording 3 consecutive heart cycles. The endocardial and epicardial borders were manually traced in the end-systolic frame for each analysis, and the software tracked the margins frame by frame automatically thereafter. Careful inspection of the tracking was conducted and manual corrections were performed if needed. In the event of unsatisfactory tracking, the segment was excluded from the analysis. Myocardial systolic strain of the LV can be assessed in 3 orthogonal directions: longitudinal, circumferential, and radial strain (Fig. 2a, b). Global longitudinal and circumferential strains are expressed as negative values; a more negative value indicates good function, while a less negative value reveals impaired function. Global radial strain is expressed as a positive value. The endocardial border of the RV free wall and septal wall was manually traced in the apical 4-chamber view. The RV longitudinal strain was calculated (Fig. 3).

Statistical analysis

All of the analyses were performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine the consistency of continuous variables with normal distribution. Homogeneity of variance was analyzed with the Levene test. Variables that had a nonhomogeneous distribution were compared using the Mann-Whitney U test. Student's t-test was used to analyze the normally distributed variables and homogeneous variables. The results were expressed as mean±SD and median value. Fisher's exact test was

used to analyze categorical variables, which were expressed as absolute values and percentages. P<0.05 was considered statistically significant.

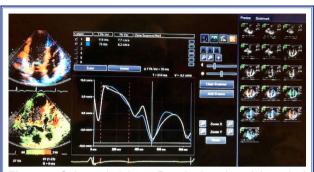


Figure 1. Color-coded tissue Doppler imaging of the apical 4-chamber view demonstrating the systolic (Sa), early (Ea), and late (Aa) diastolic tissue velocities of mitral and tricuspit annular sites.

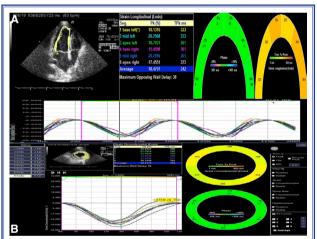


Figure 2. (A) Left ventricular longitudinal strain curves from 6 segments of the apical 4-chamber view are seen. The curves are negative, representing the segmental shortening during systole; **(B)** A dotted curve illustrates the left ventricular circumferential strain of the mid short-axis cut plane.

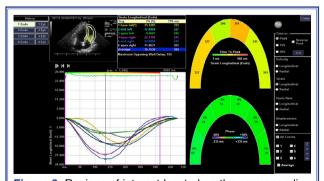


Figure 3. Regions of interest located on the corresponding right ventricular segmental longitudinal strain curves. Note that the right ventricular longitudinal strain is negative because it represents shortening during systole.

RESULTS

The groups were similar with regard to age and gender. A comparison of the clinical and biochemical parameters of the study groups is presented in Table 1. The mean systolic and diastolic blood pressure was significantly lower in the liver transplant candidates than in the controls. The mean cholesterol level was lower in the liver transplant candidates (Table 1).

The 2D and Doppler echocardiographic measurements are presented in Table 2. There was no significant difference in the EF between groups, but the

end-diastolic volume and end-systolic volume were higher in the liver transplant candidates than in the controls (Table 2). Additionally, the LV mass index measurement was higher in the liver transplant candidates than in the controls. The Ea and Ea/Aa ratio were significantly lower in the liver transplant candidates when compared with the control group and the E/Ea ratio, as a means of LV end-diastolic pressure, was greater in the liver transplant candidates than the controls. The Sa was significantly lower in the liver transplant candidates than in the controls at the lateral annulus and the septal annulus. The LV mean

Table 1. Baseline clinical charecteristics and biochemical parameters of the groups			
	Cirrhosis	Control	р
	(n=40)	(n=26)	
Age (years)	46.2±10.1	42.2±8.6	0.001
Male/female	28/12	16/10	0.005
Body surface area (m²)	1.8±0.1	1.8±0.2	0.008
Systolic blood pressure (mmHg)	109±11	118±8	0.003
Diastolic blood pressure (mmHg)	67±7	72±8	0.001
Heart rate (beats/min)	73±11	74±8	0.007
Laboratory findings			
Fasting glucose (mg/dL)	97±14	90±8	0.007
Creatinine (mg/dL)	0.7±0.2	0.8±0.2	0.006
Total cholesterol (mg/dL)	114±32	155±66	0.001
High-density lipoprotein cholesterol (mg/dL)	35±13	49±13	0.001
Low-density lipoprotein cholesterol (mg/dL)	63±20	109±20	< 0.001
Triglyceride (mg/dL)	79±38	130±44	<0.001

Table 2. Left ventricle 2-dimensional and Doppler echocardiographic measurements			
	Cirrhosis	Control	р
	(n=40)	(n=26)	
Left ventricle end-diastolic diameter (cm)	4.7±0.3	4.5±0.3	0.001
Septum wall thickness (cm)	1.07±0.10	0.99±0.09	0.003
Left ventricle posterior wall thickness (cm)	1.06±0.10	0.99 ± 0.09	0.006
Left atrial diameter (cm)	3.8±0.4	3.4±0.3	<0.001
Left ventricle end-diastolic volume (mL)	107.2±18	89.9±15.6	<0.001
Left ventricle end-systolic volume (mL)	45.5±9.3	35.1±8.3	<0.001
Left ventricle ejection fraction (%)	59.7±2.7	60.5±2.8	0.002
Early/late diastolic velocity	1.2±0.3	1.2±0.3	0.009
Mitral deceleration time (ms)	215.3±31.4	206±38.2	0.004
Isovolumic relaxation time (ms)	106.6±16.2	106.1±9.0	0.009
Left ventricle mass index (g/m²)	106.7±16.8	88.5±11.3	<0.001

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longitudinal strain was significantly lower in the liver transplant candidates when compared with the control group in both the apical 4- and 2-chamber views. The LV mean circumferential strain was not significantly different between the groups. However, the LV mean radial strain was significantly lower in the liver transplant candidates than in the controls (Table 3).

The RV diastolic diameter and right atrium diameter were greater in the liver transplant candidates than in the controls (Table 4). The RV Ea velocity and Ea/Aa ratio were significantly lower in the liver transplant candidates than in the controls, and the E/Ea

ratio, as a means of RV end-diastolic pressure, was higher in the liver transplant candidates compared with the controls. The RV mean Sa velocity and RV mean longitudinal strain were significantly lower in the liver transplant candidates than in the controls. Furthermore, the MPI value of the RV was greater in the liver transplant candidates than in the controls (Table 4).

DISCUSSION

STI is a newer imaging modality able to objectively quantify regional and global biventricular functions.

Table 3. Left ventricle color-coded tissue Doppler imaging and strain measurements			
	Cirrhosis	Control	р
	(n=40)	(n=26)	
Left ventricle septal Sa (cm/s)	7.1±1.1	7.6±0.7	0.004
Left ventricle lateral Sa (cm/s)	7.1±1.5	8.1±0.7	0.008
Left ventricle mean annular Sa (cm/s)	7.1±1.0	7.8±0.5	0.004
Left ventricle septal Ea (cm/s)	6.0±2.1	7.2±1.9	0.001
Left ventricle lateral Ea (cm/s)	5.3±2.3	7.7±1.4	<0.001
Left ventricle mean annular Ea (cm/s)	5.6±2.0	7.4±1.1	< 0.001
Left ventricle E/Ea	18.0±9	10.5±2	< 0.001
Left ventricle Ea/Aa	0.9±0.3	1.4±0.6	<0.001
Left ventricle mean longitudinal strain (%)			
Apical 4-chamber	-16.0±3.2	-17.6±2.2	0.003
Apical 2-chamber	-16.2±3.3	-18.7±2.1	0.002
LV mean circumferential strain (%)	-23.4±3.2	-24.5±3.0	0.001
LV mean radial strain (%)	45.4±10.7	52.7±10.8	0.001

Aa: Late diastolic color-coded tissue velocity; Ea: Early diastolic color-coded tissuevelocity; Sa: Peak systolic color-coded tissue velocity.

Table 4. Right ventricle echocardiographic measurements				
	Cirrhosis	Control	р	
	(n=40)	(n=26)		
Right ventricle end-diastolic diameter (cm)	2.9±0.3	2.7±0.2	0.004	
Right atrial diameter (cm)	3.5±0.3	3.3±0.2	0.003	
Tricuspid E/A	1.13±0.2	1.25±0.2	0.001	
Right ventricle mean Sa (cm/s)	7.0±1.1	7.9±0.6	0.007	
Right ventricle mean Ea (cm/s)	6.9±1.4	8.1±0.9	0.004	
Right ventricle E/Ea	9.0±2.8	6.9±1.6	0.007	
Right ventricle Ea/Aa	1.0±0.6	1.5±0.5	0.004	
Right ventricle mean longitudinal strain (%)	-19.2±3.5	-21.5±3.6	0.003	

Aa: Late diastolic color-coded tissue velocity; A: Late diastolic velocity; Ea: Early diastolic color-coded tissue velocity; E: Early diastolic velocity; Sa: Peak systolic color-coded tissue velocity.

We evaluated LV and RV function in liver transplant candidates with ESLD using VVI, a 2D-strain imaging method based on speckle tracking.

The EF measurement was similar in the 2 groups. We determined that impairment of systolic LV function in patients with ESLD could be more sensitively detected with STI than conventional echocardiography. Previous studies have indicated that STI is more sensitive than conventional echocardiography in detecting subclinical ventricular dysfunction in various clinical disorders.[7-10] Our results showed that this subclinical impairment was mostly related to longitudinal and radial rather than circumferential deformation mechanics, which is consistent with the early stages of myocardial damage. Global longitudinal strain is first affected because the longitudinally orientated subendocardial fibers are most susceptible to damage.[11] Sub-endocardial fibers generate the most significant contribution to longitudinal function. Global longitudinal strain also supports a prognostic evaluation with a good clinical value for predicting heart failure.[12] Additionally, it has been shown that global longitudinal strain is superior to LV EF and all other conventional echocardiographic parameters in predicting mortality.[13] The middle and sub-epicardial layers further contribute to thickening and to radial and circumferential function. These fibers are a key determinant of preserved global LV function.[14] This may explain why circumferential deformation was not reduced in our study. Furthermore, we found that although the EF of these patients was normal, the Sa was seen to be reduced with cTDI. This finding supports the presence of subclinical myocardial dysfunction. Previous studies have shown that LV diastolic dysfunction is common in patients with cirrhosis. [2,15,16] In our study, we identified diastolic dysfunction on cTDI echocardiography in patients with ESLD. We also found a greater LV mass index value, suggesting diastolic dysfunction in these patients.[17] This impairment cannot be detected with conventional Doppler, possibly due to hypervolemia and hyperdynamic circulation in these patients.

All invasive and noninvasive imaging techniques that can evaluate the structure and functions of the RV have important limitations due to the complex RV geometry. Volume calculation and estimation of EF are not ideal for the assessment of RV function. Little is known about the effects of ESLD on RV function.

Our study found an increase in RV and right atrium diameters in patients with ESLD compared with the controls, similar to the results of other studies measuring with echocardiography.[18,19] This could be explained by an increased venous return to the right heart caused by the development of portosystemic collaterals to counterbalance the increased intrahepatic vascular resistance to portal blood flow.[10,20] In our study, liver transplant candidates had a significantly higher RV MPI. MPI, which is an index of sensitive and load-independent cardiac dysfunction, shows subtle RV systolic and/or diastolic abnormalities.[21-23] Similarly, the diastolic and systolic indices of cTDI echocardiography revealed impairment of RV function in patients with ESLD. These findings suggest impaired diastolic and systolic RV function and increased RV filling pressure in liver transplant candidates with ESLD. Hepato-pulmonary syndrome and pulmonary hypertension may adversely affect RV myocardial function; therefore, we excluded these conditions. Additionally, the RV mean longitudinal strain was significantly lower in the liver transplant candidates. This subclinical impairment of systolic RV function in liver transplant candidates with ESLD can be detected using VVI strain imaging. Detailed evaluation of RV functions in these patients can be very important because studies have shown that RV functions are superior to LV functions in predicting poor clinical outcomes in these patients.^[24]

There are several limitations to this study that should be taken into consideration. Our control group was relatively small. The analyses performed require offline processing and cannot be performed during live study. It was ideal to evaluate systolic function in patients before and after liver transplantation, but echocardiography was not performed after liver transplantation. Only 2D-echocardiographic parameters were used to evaluate function. Novel 3D-strain echocardiography was not used. For longitudinal strain, we analyzed data from the apical 4- and 2-chamber views. Additional analysis of the apical long-axis view provides optimal information for longitudinal strain. All of the images were analyzed by a single researcher, but intra-observer variability was not recorded at the time of the study. RV function was not evaluated using methods such as tricuspid annular plane systolic excursion, 2D fractional area change, and 3D EF measurement.

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Conclusion

STI has gained wide clinical use in recent years and 2D-STI allows for rapid and accurate analysis of systolic ventricular function in the longitudinal, radial, and circumferential directions. The technique is able to detect subtle changes in myocardial function at an early stage, even before there is a visible decrease in conventional echocardiographic parameters. Systolic functions appeared to be normal in cirrhotic cardiomyopathy when assessed by 2D- and conventional Doppler echocardiography, possibly due to hypervolemia and hyperdynamic circulation in these patients at rest. This study demonstrated that liver transplant candidates with ESLD had impaired LV and RV function measured at an early stage. VVI 2D-strain imaging and cTDI are sensitive tools that can detect subclinical LV systolic and diastolic function in liver transplant candidates when conventional echocardiography measurements at rest is normal.

Ethics Committee Approval: The study protocol was approved by the Başkent University Clinical Research Ethics Committee (KA08/145).

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Keywords: Echocardiography; end-stage liver disease; strain.

Anahtar sözcükler: Ekokardiyografi, son dönem karaciğer hastalığı; strain.