Non alcoholic steatohepatitis is associated with subclinical impairment in left ventricular function measured by speckle tracking echocardiography

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ABSTRACT

Objective: Nonalcoholic steatohepatitis (NASH) is a part of histological spectrum of nonalcoholic fatty liver disease (NAFLD). Higher incidence of cardiovascular mortality has been reported in studies including patients with NAFLD. Impaired myocardial function can be detected by a novel echocardiographic method called speckle tracking echocardiography (STE) when conventional methods were normal.

Methods: Twenty-eight biopsy-proven NASH patients (mean age 41.6±9.8, 16 male) without hypertension and diabetes mellitus were included in study. All patients underwent transthoracic echocardiography. Offline analyses of images was performed and strain (S), strain rate (SR) parameters compared between NASH patients and controls. Statistical analysis were done by independent samples t test between groups and a multiple linear regression model was used to identify the statistical significance of relationships between selected variables.

Results: R_{SR-S} values were similar but R_S, R_{SR-E}, $R_{SR-E/A}$ values were significantly lower and R_{SR-A} was higher in the NASH patients. There were no significant differences in C_S, C_{SR-S}, C_{SR-E}, C_{SR-A} and $C_{SR-E/A}$ values among the two groups. The most impressive results were obtained from longitudinal strain and strain rate parameters. L_S, L_{SR-S}, L_{SR-E}, L_{SR-A}, values were significantly lower in NASH group when compared with healty controls. Linear regression analysis showed that RS and LS was not associated with diastolic blood pressure, total cholesterol and LDL cholesterol.

Conclusion: The LV longitudinal and radial systolic functions may be deteriorated in patients with NASH even in the absence of apparent decrease in the LV ejection fraction. STE may be useful in detecting preclinical LV impairment in patients with NASH. *(Anatolian J Cardiol 2015; 15: 137-42)*

Key words: nonalcoholic steatohepatitis, speckle tracking echocardiography, subclinical myocardial dysfunction, nonalcoholic fatty liver disease

Introduction

Nonalcoholic steatohepatitis (NASH) is a part of histological spectrum of nonalcoholic fatty liver disease (NAFLD) and may progress to cirrhosis in 15-20% of individuals within one or two decades (1). Conventional and novel risk factors for cardiovascular disease are commonly observed in NAFLD patients. Higher incidence of cardiovascular mortality and severity of coronary artery disease reported in studies including patients with NAFLD (2, 3). In these studies NAFLD was associated with abnormal diastolic functions and left ventricular structure (4). NASH is an advanced form of NAFLD, characterized with histological changes in liver. Cardiovascular morbidity and mortality is increased in patients with NASH.

2-D speckle tracking is a novel echocardiographic method that determines myocardial deformation from continuous frame-by-frame tracking of speckles called as 2-D speckle tracking echocardiography (2-D STE) which is angle independent and can assess the magnitude and timing of regional and global ventricular deformation in different directions (5).

Previous studies usually investigated NAFLD patients who were diagnosed by, a qualitative assessment method, abdominal ultrasound, and conventional echocardiographic methods like tissue Doppler echocardiography (4, 6). Differently in this study, we aimed to investigate the presence of subclinical myocardial systolic and diastolic dysfunction using 2-D STE, in patients with NASH diagnosed by liver biopsy.

Methods

Twenty-eight NASH patients (mean age 41.6±9.8, 16 male) who were examined at the Kayseri Education and Research

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Accepted Date: 17.01.2014 **Available Online Date:** 08.04.2014

DOI:10.5152/akd.2014.5212

Hospital Gastroenterology outpatient clinic and diagnosed by liver biopsy were included in this study. 28 sex and age matched healthy volunteers without abnormal biochemical and ultrasonography were selected as control group. Informed consent forms were obtained from every individual enrolled and the study was approved by the local Ethics Committee of Kayseri Education and Research Hospital.

The exclusion criteria were as follows; angina and angina equivalent symptoms, history of abnormal cardiovascular stress test and abnormal myocardial scintigraphy, an LVEF lower than 50%, individuals with structural heart disease, a documented history of coronary and peripheric vascular diseases, diabetes mellitus, body mass index (BMI) >30 kg/m^2, hypertension; defined as a systolic blood pressure value of >140 mm Hg and diastolic blood pressure value of >90 mm Hg after averaging three separate blood pressure measurements taken at 10 minute intervals and patients receiving antihypertensive treatment, restrictive and obstructive pulmonary disease, individuals with systemic and metabolic diseases that could adversely affect the cardiac structure and functions, and smoking.

All individuals' blood pressures, pulses, and anthropometric measures were recorded before echocardiography. BMI were derived from anthropometric measures. Biochemical parameters were obtained from previous recording of venous blood samples drawn after an 8 hour fasting period at gastroenterology outpatient clinic. HOMA-IR was calculated by formula.

Echocardiography was performed in the left lateral decubitus position with the GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) ultrasound and a 3S-RS (3.5 mhz) probe. All echocardiographic examinations were performed by two experienced cardiologists who were unaware of the clinical data of the groups. Images were obtained from parasternal and apical view using 2-D, M-Mode and Doppler echocardiographic techniques. The 2-D, M-mode and Doppler echocardiographic examinations were performed according to the guidelines of American Society of Echocardiography (7). The left atrial (LA) volume was determined using the biplane area-length method after measuring the area and the long-axis length of the LA at ventricular end-systole in the apical 4-chamber and 2-chamber views. The LA volume was then calculated according to the biplane area-length formula. The LA volume index was defined after the correction for body surface area (7).

Tissue Doppler imaging (TDI) was performed from the apical four-chamber view using a pulsed-wave Doppler with a 3 mm sample volume placed on the septal and lateral mitral annulus. All of the annular velocities and time intervals of tissue Doppler analysis were calculated as an average of the two annular sites. Pulsed-wave TDI examinations were performed according to the guidelines of American Society of Echocardiography (8). The ratios between the mitral early diastolic flow velocity (E), the mitral annular early diastolic myocardial velocity (E'). The averages of three consecutive cycles were measured for all echocardiographic data.

A software package (Echopac PC, version 8.0, GE Healthcare) was used to perform offline analyses of STE from apical and parasternal short-axis views. Standard grayscale 2-D images were obtained from the apical 4, 2, 3 chamber views and the parasternal short-axis views at the papillary muscle level at a frame rate of 70-90 frame(s). Myocardial strain ($_S$) and strain rate ($_{SR}$) were measured as previously described (9). After end-expiratory breath holding 3 consecutive cardiac cycles were recorded and stored for the offline analysis. Endocardial border of the left ventricule (LV) was traced manually at the end of the end-systolic frame. Software automatically created a region of interest on the entire wall and selected natural acoustic markers. Via frame by frame tracking of these markers during the cardiac cycle, measurement of S and SR at any point of the myocardium was done. The circumferential strain (C_S), systolic strain rate (C_{SR-S}), early diastolic strain rate (C_{SR-E}), and the late diastolic strain rate (C_{SR-A}) values of the LV were obtained using the graphics generated by the software through the evaluation of the analyses belonging to the six segments. Because the graphics created by the program to depict the circumferential functions could not be generated for the radial functions following the analysis, the arithmetical average of the radial strain and the strain rate values were found by calculating the arithmetic average of the radial strain (R_S), systolic strain rate (R_{SR-S}), early diastolic strain rate (R_{SR-E}) and the late diastolic strain rate (R_{SR-A}) values belonging to the six segments. The longitudinal strain (L_S), longitudinal systolic strain rate (L_{SR-S}), early diastolic strain rate (L_{SR-E}) and the late diastolic strain rate (L_{SR-A}) were measured from 6 LV walls from the apical 4, 2, 3 chamber views recordings. The averages of these measurements were used for the comparison of the NASH patients with the controls. Radial strain (R_S), radial systolic strain rate (R_{SR-S}), early diastolic strain rate (R_{SR-E}) and the late diastolic strain rate (R_{SR-A}) were obtained from the parasternal LV short-axis view at the level of the papillary muscles. The C_S, C_{SR-S}, C_{SR-E}, C_{SR-A} were also obtained from the same views and the calculation of average values used for the compassion.

Statistical analysis

All analyses were carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were given as mean±standard deviation; categorical variables were defined as percentages. The variables were investigated using Kolmogorov-Smirnov test to determine whether or not they are normally distributed. Independent samples t test was used to compare continuous variables between the two groups. Nonparametric values were compared with Mann-Whitney U test. Chi-square test was used to compare categorical data. A multiple linear regression model was used to identify the statistical significance of relationships between selected variables and R_S and L_S. The Blant-Alman analysis method was used to determine inter and intraobserver variability. A two tailed p value <0.05 was considered as significant.

Results

A total of 56 subjects consisting of 28 healthy individuals and 28 NASH patients were evaluated in the study. Detailed demographic, clinical, biochemical variables of the two groups are presented in Table 1. Detailed parameters of 2-D, pulse Doppler and TDI of the two groups are given in Table 2. Isovolumic relaxation time (IVRT) and deceleration time (DT) were higher in NASH patients. Mean S and mean E tissue Doppler values were lower in patients with NASH but E/E' and E/A ratio were similar between two groups.

Systolic, diastolic strain and strain rate parameters

Detailed 2D-STE values of the all groups are given in Table 3. R_S was lower in the NASH group than in the healthy individuals and differences were statistically significant. R_{SR-S} values were similar but R_{SR-E}, $R_{SR-E/A}$ values were significantly lower and R_{SR-A} was higher in the NASH patients. There were no significant differences in C_S, C_{SR-S}, C_{SR-E}, C_{SR-A} and $C_{SR-E/A}$ values among the two groups. The most impressive results were obtained from longitudinal strain and strain rate parameters. L_S, L_{SR-S}, L_{SR-E}, L_{SR-A}, values were significantly lower in NASH group when compared with healthy controls (Table 3). Comparison of L_S, C_S and R_S were given in Figure 1. Linear regression analysis showed that R_S was not associated with diastolic blood pressure (Coefficient b: 0.053, p=0.694), total cholesterol (Coefficient b: 0.014, p=0.947) and LDL cholesterol (Coefficient b: 0.170, p=0.383). Also L_S was not associated with diastolic blood pressure (Coefficient b: 0.028, p=0.709), total cholesterol (Coefficient b: 0.470, p=0.686) and LDL cholesterol (Coefficient b: 0.030, p=0.781) (Table 4, 5).

Discussion

Results of present study demonstrated that longitudinal and radial strain were lower in NASH patients.

Insulin resistance (IR), is the main pathophysiological mechanism of NASH (10). Hepatic steatosis leads to hepatic IR and impaired suppression of hepatic glucose production, which leads to hyperglycemia in NAFLD patients. Subsequently compensatory hyperinsulinemia and worsening of systemic and cardiac IR occurs (11-13). Myocardial IR affects cardiomyocytes in several mechanisms. Firstly, products of free fatty acids (FFA) excess metabolism (14) generates a well described phenomenon "cardiac lipotoxicity". In patients with nonischemic chronic heart failure with obesity and/or diabetes, lipotoxicity also plays an essential role in the pathogenesis of cardiomyopathy which is a leading cause of death (15-17). Especially, in diabetic patients liver fat content independently indicates myocardial IR and impaired coronary functional capacity (18). Present study investigated nondiabetic patients, but HOMA-IR levels indicating IR were higher than the control group as expected. We can speculate that in NASH myocardial impairment may occur due to myocardial IR. Secondly, ceramide accumulation formed via de novo synthesis from FFA, plays a central role in apoptosis of cardiomyocytes. Structural alterations in mitochondria can reduce cardiac function by providing an insufficient supply of ATP to cardiac myocytes or by increasing reactive oxygen spe-

Table 1. Demographic, clinical, biochemical variables of the NASH and control groups

	NASH	Control	*P*
Age	41.6±9.8	41.2±9	0.877
BMI, (kg/m^2)	27.7±1.6	26.7±1.7	0.053
HOMA-IR	5.29±4.3	2.1±1.3	<0.001
Systolic BP, mm Hg	120.7±9.3	120.3±12	0.902
Diastolic BP, mm Hg	79.2±5	75.0±9.5	0.042
Fasting glucose, mg/dL	95.1±18.1	90.0±6.6	0.171
Total cholesterol, mg/dL	233.4±46.2	198.3±15.9	<0.001
LDL-cholesterol, mg/dL	149.0±35	129.8±21.8	0.022
HDL-cholesterol, mg/dL	47.0±9.4	45.4±7.3	0.482
Trigliseride, mg/dL	217.0±123.5	167.3±47.9	0.063
AST, U/L	42.7±9.6	33.0±5.5	<0.001
ALT, U/L	44.5±9.3	33.4±6.2	<0.001
GGT, U/L	64.7±42.7	39.2±8.8	=0.04

Data are expressed as mean±SD
ALT - alanine transaminase; AST - aspartic acid transaminase; BMI - body mass index; BP - blood pressure; GGT - gamma-glutamyltransferase; HDL - high density lipoprotein; LDL - low density lipoprotein

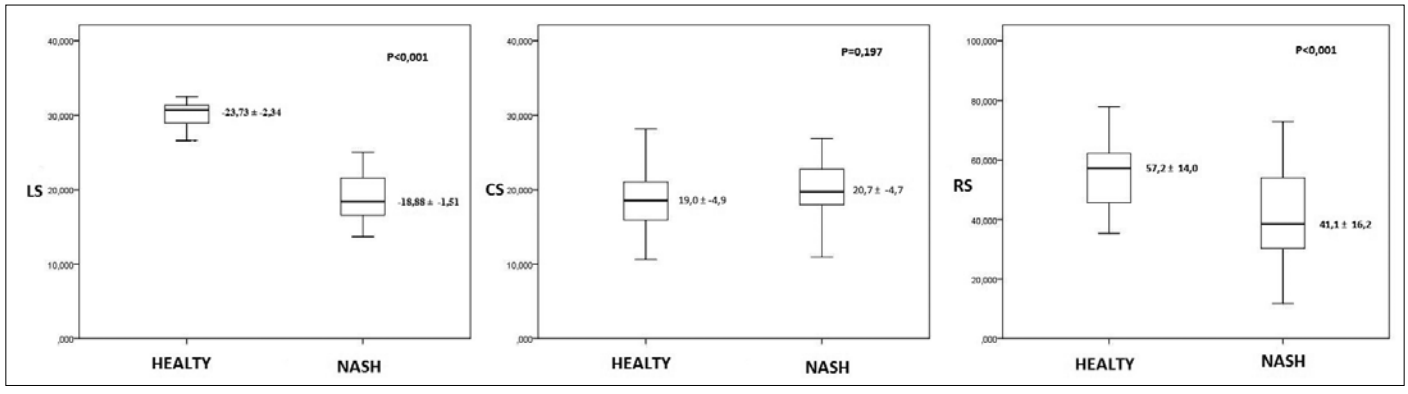

Figure 1. Comparison of longitudinal strain (LS), circumferential strain (CS) and radial strain (RS)

Table 2. 2-D, M-mode, Doppler and tissue Doppler echocardiography parameters of the patients and the control group

	NASH	Control	*P*
LVDD, mm	46.5±4.7	45.9±3.8	0.624
LVSD, mm	29.1±3.6	29.0±2.9	0.936
IVSDD, mm	9.9±1.3	8.6±0.8	<0.001
PWDD, mm	10.2±1.4	8.7±0.8	<0.001
EF, %	66.7±5.2	65.7±2.4	0.385
LA, mm	33.8±3.1	32.0±3.4	0.043
LAVI, mL/m^2	19.6±1.7	18.8±1.9	0.107
Mit E, m/s	0.72±0.15	0.80±0.14	0.038
Mit A, m/s	0.67±0.14	0.67±0.16	0.897
Mit E/A, ratio	1.13±0.39	1.23±0.30	0.242
E/E', ratio	6.93±1.6	6.38±1.33	0.170
Mean S, m/s	0.08±0.01	0.12±0.02	<0.001
Mean E, m/s	0.11±0.03	0.13±0.02	0.012
IVRT, ms	83.3±13.0	70.6±12.4	0.001
IVCT, ms	58.2±14.5	63.1±7.1	0.118
DT, ms	219.6±45.4	160.1±31.3	<0.001

Data are expressed as mean±SD
DT - deceleration time; E/A - ratio between diastolic early and late-diastolic mitral inflow velocities; E/E' - ratio between early-diastolic mitral inflow velocity and early-diastolic annular velocity; EF - ejection fraction; IVCT - isovolumic contraction time; IVSDD - interventricular septum diastolic thickness diameter; IVRT - isovolumic relaxation time; LA - left atrium; LAVI - left atrial volume index; LVDD - left ventricular diastolic diameter; LVSD - left ventricular systolic diameter; Mean S - systolic velocity on tissue Doppler echocardiography; Mean E - early diastolic velocity on tissue Doppler echocardiography; PWDD - posterior wall diastolic thickness diameter

Table 4. Linear regression analysis showing relationships between several variables and R_S

Variables	Coefficient b	95% CI	*P*
Diastolic BP	0.053	0.607-0.467	0.694
Total cholesterol	0.014	0.195-0.182	0.947
LDL-cholesterol	0.170	0.317-0.124	0.383

R_S - radial strain

Table 5. Linear regression analysis showing relationships between several variables and L_S

Variables	Coefficient b	95% CI	*P*
Diastolic BP	0.028	0.104-0.152	0.709
Total cholesterol	0.470	0.050-0.033	0.686
LDL-cholesterol	0.030	0.042-0.055	0.781

L_S - longitudinal strain

cies (ROS) production, which has been associated with increased apoptosis, DNA damage and decreased DNA repair (19). Furthermore, ROS and reactive nitrogen species (RNS) triggers the activation of inflammatory pathways (20, 21). Conventional echocardiografic imaging parameters of left ventricular (LV) function like ejection fraction (EF) may be in normal limits in patients with NAFLD. In addition to conventional echocardiography, studies inspecting alterations of myocardial energy metabolism by magnetic resonance spectroscopy also showed that LV morphology and function was normal in non-diabetic NAFLD patients (22). However, subclinical LV impairment due to IR can be detected by advanced echocardiographic features like STE in NASH patients without morbid obesity, hypertension and diabetes, as in our study.

Table 3. Global strain and strain rate parameters of the patients and the control group

	NASH	Control	*P*
Radial			
S (%)	41.1±16.2	57.2±14.0	<0.001
SRS (1/s)	2.34±0.75	2.30±0.61	0.789
SRE (1/s)	-1.63±-0.57	-2.23±-0.72	0.001
SRA (1/s)	-1.85±-0.76	-1.38±-0.55	0.011
SR E/A	1.07±0.62	1.96±1.12	0.001
Circumferential			
S (%)	-20.7±-4.7	-19.0±-4.9	0.197
SRS (1/s)	-1.32±-0.43	-1.18±-0.48	0.252
SRE (1/s)	1.42±0.62	1.52±0.71	0.558
SRA (1/s)	0.83±0.45	0.70±0.44	0.284
SRE/A	2.04±0.90	2.52±1.13	0.082
Longitudinal			
GLS (%)	-18.88±-1.51	-23.73±-2.34	<0.001
GLS2CH	-18.52±-2.32	-23.79±-3.11	<0.001
GLS3CH	-19.26±-2.10	-23.19±-2.95	<0.001
GLS4CH	-18.63±-1.95	-24.21±-2.82	<0.001
SRS (1/s)	-1.14±-0.20	-1.73±-0.28	<0.001
SRE (1/s)	1.20±0.38	2.35±0.55	<0.001
SRA (1/s)	0.88±0.26	1.47±0.37	<0.001
SRE/A	1.45±0.55	1.68±0.53	0.106

Data are expressed as mean±SD and n (%)
A - late diastolic; E - early diastolic; GLS - global longitudinal strain; GLS2CH-GLS3CH-GLS4CH - Global longitudinal strain of apical-4, 2, 3 chambers; S - systolic; S (%) - strain; SR - strain rate

The conventional indices of global LV systolic and diastolic function, like EF and volumes have some disadvantages. These are load dependency, measurement errors, insufficient image quality. TDI is an other useful echocardiographic technique employing the Doppler principle to measure the velocity of myocardial segments and other cardiac structures which is load independent. But TDI also has some limitations, like angle dependency of the ultrasound beam, the complex rotational and translational movements of the heart. 2D-STE is a new imaging modality which calculates myocardial velocities and deformation parameters like strain and strain rate. Strain is a dimensionless index of myocardial deformation and is usually expressed in percent (%). Strain rate is the difference of strain in a time interval. Since STE was introduced in 2004, it is well known that strain and strain rate parameters provide important insights into

systolic and diastolic function, ischaemia, myocardial mechanics and many other pathophysiological conditions of the heart. When left ventricular impairment begins, compensatory mechanisms can still sustain the normal stroke volume. 2D-STE can detect reduced contractility in patients with normal ejection fraction before changes in myocardial tissue velocities and other traditional parameters of systolic function (23).

Previous studies mostly included NAFLD patients who were diagnosed and scored by ultrasonography features (24). And demonstrated that non-diabetic subjects with NAFLD had early alterations especially in LV diastolic function detected by TDI. Some of them did not found any relationship between NAFLD and systolic tissue velocities (4). Fotbolcu et al. (25) reported LV diastolic and systolic dysfunction by TDI, and their parameters represented lower mean S, E' tissue velocities and longer IVRT compared with control subjects as in ours. But we found mean S values lower than their findings and their patients selected to study were NAFLD patients diagnosed by abdominal ultrasonography.

In a recent study in obese pediatric patients, investigators demonstrated that obese adolescents with NAFLD have greater abnormalities in cardiac function, manifested by decreased systolic and diastolic myocardial strain and strain rate than obese adolescents who have normal IHTG content. In addition, obese adolescents with NAFLD were independent of traditional cardiac risk factors (26). Our results demonstrated that in addition to measurement of LV global L_S and L_{SRS}, R_S by speckle tracking analyses were also lower when compared with control subjects. Furthermore, R_{SRE} and $R_{SRE/A}$ were also reduced which indicate LV diastolic dysfunction (27). These 2D-STE results may reflect the consequence of further impairment of LV systolic and diastolic function compared with studies investigated NAFLD patients. Because of advanced necroinflammatory situation, advanced impairment of ventricular function may be detected by STE in NASH. Furthermore progression of NAFLD and cardiac influences may be recognized noninvasively by STE.

In another study by STE, Bonapace et al. (28) reported that NAFLD patients had significantly higher $L_{E/SR-E}$ and tended to have lower L_{SR-E} and L_{SRA} by measurements of LV global longitudinal strain and strain rate by speckle tracking analyze. But were not statistically significant except $L_{E/SRE}$ which were a parameter of diastolic function. However, patients included in that study were NAFLD patients with type 2 diabetes and they concluded that NAFLD may contribute to impairment of LV function which was already impaired in type 2 diabetes (28). Hallsworth et al. (29) examined cardiac status in a clinical group of NAFLD patients, using the combined techniques at 3.0T of phosphorus spectroscopy, cardiac tagging and cine MRI to measure cardiac energetics, strain and morphology. They concluded that in the absence of overt cardiac disease, longitudinal shortening was reduced. Differently, NAFLD was defined as >5% intrahepatic lipid.

When compared with previous studies, our study group is a more specific, biopsy-proven necroinflammatory form of NAFLD without type 2 diabetes. Reduced radial and longitudinal strain/strain rate datas evidently shows that as the disease advances, additional impairment in LV systolic function occurs. Mediators from the steatotic-inflamed liver, the contribution of insulin resistance, ROS, RNS and products of FFA excess metabolism in NASH may yield to further cardiac impairment (28).

There were significant difference in the level of cholesterol, LDL and diastolic BP between the groups of control and the patients. But linear regression analyses revealed that level of cholesterol, LDL and diastolic BP were not associated with R_S and L_S.

Study limitations

The main limitation of this study was the low number of patients, but patients considered in this study were biopsy proven and without cardiovascular risk factors. Although there were not differences between systolic and diastolic blood pressures, we did not take 24-h ambulatory blood pressure recordings. Therefore we are not able to evaluate possible increases in blood pressure in NASH patients. The aim of our study was to evaluate the relationship between the NASH and the myocardial function by using the 2D-STE method, other biochemical parameters of myocardial function like brain natriuretic peptide did not evaluated. Comparison of another group of patients which includes simple hepatic steatosis with other groups may reflect the progression of myocardial influences in NAFLD patients.

Conclusion

It may be concluded that the LV longitudinal and radial systolic functions may deteriorate in patients with NASH without an apparent decrease in the LVEF. According to our results, insulin resistance in NASH could be the main mechanism for such LV changes. Therefore, in patients with NASH, besides the conventional echocardiography and TDI methods, the presence of subclinical myocardial dysfunction can be determined in detail during the early stages through the 2D-STE method.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - A.O.B., B.Ş.; Design - H.A., A.K., H.K.; Supervision - H.A.; Resource - A.O.B., B.Ş.; Materials - A.O.B., B.Ş.; Data collection &/or processing - Y.D., A.E., H.A.; Analysis &/or interpretation - A.O.B., B.Ş., R.E.A.; Literature search - H.S., Y.D.; Writing - A.O.B.; Critical review - B.Ş., R.E.A.

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