Original Paper

Contribution of Modern Echocardiographic Techniques in the Detection of Subclinical Heart Dysfunction in Young Adults with Non-Alcoholic Fatty Liver Disease

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ABSTRACT: Non-alcoholic fatty liver disease affects about 30% of the population and it has a growing tendecy with the increasing incidence of obesity. Currently, a large amount of clinical evidence has shown that cardiovascular disease represents the main cause of mortality in patients suffering from non-alcoholic fatty liver disease. Objective: In this study we investigated the structural and functional changes of the left ventricle in young adults with hepatic steatosis using modern echocardiographic techniques. Methods:By using tissue Doppler imaging and also Speckle tracking echocardiography the left ventricle systolic function was assessed. Results: All patients included in the study had a normal left ventricular ejection fraction but, when the longitudinal function of the left ventricle was assessed using the tissue Doppler technique (maximum systolic velocity S) statistically significant differences were found in both the group of patients with non-alcoholic fatty liver as well as in the group of patients associated with diabetes. Using speckle tracking echocardiography, we found a statistically significant decrease of the global longitudinal strain in the endocardium, in the group of patients with non-alcoholic liver disease but also in the group of those with diabetes. The overall longitudinal strain at the myocardium was significantly reduced only in the group of patients with non-alcoholic fatty liver disease and diabetes, while the overall longitudinal strain at the epicardium showed no changes in any of the groups studied. Also, no changes were observed at the circumferential strain. Conclusion: Non-alcoholic fatty liver disease, diagnosed in asymptomatic young adults may be a risk factor for remodeling the left ventricle over time, being associated with subclinical myocardial dysfunction, regardless of the presence of other cardiovascular risk factors.

KEYWORDS: *Left ventricular dysfunction, non-alcoholic fatty liver disease, global longitudinal strain, circumferential strain, tissue Doppler imaging.*

Introduction

Non-alcoholic fatty liver disease, a common chronic disease of the liver, frequently affecting patients belonging to all age groups is a serious medical condition because of the obesity incresing prevalence. It is definedby the infiltration of hepatic cells with fat, while thealcohol consumption is under 30g (three units) in men and 20g (two units) in women, having no other causes of liver damage.

Non-alcoholic fatty liver disease is represented by a set of clinical-biological manifestations: simple steatosis, characterized by an excess of triglycerides in the liver and steatohepatitis with potential evolution to liver cirrhosis and hepatocellular carcinoma. Non-alcoholic steatohepatitis is a more aggressive form (the inflammatory component along with steatosis), associating a higher risk of both heart failure and mortality in comparison with simple steatosis [1].

In addition, non-alcoholic fatty liver associates a high risk for coronary heart disease, different arrhythmias and also dysfunction of the left ventricle, and that is why it represents arisk factor for subclinial heart dysfunction. It has also been shown that this condition increases the insulin resistance and contributes to atherogenic dyslipidemia and, in consequence, it was linked to obesity and high blood pressure. It is currently considered that the hepatic symptoms of this syndrome that affects the metabolism, make patients more prone to early atherosclerosis. Releasing ddifferent mediators (proinflammatory, procoagulant and profibrogenic) plays an important role in thepathophysiology of the cardiac complications [2-4].

Tissue Doppler imaging uses the Doppler principle to quantify myocardial velocities. Currently, the technique is available on most

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modern echocardiographic systems and has been introduced as a standard method of exploring LV function.

Speckle tracking echocardiography, which represents a state-of-the-art non-invasive imaging technique, is used in order to evaluate the myocardial function either globally or regionally, is based on the recognition on the two-dimensional image of *speckles* (essentially a myocardial wall imprint), and dynamic tracking of each point identified, throughout the cardiac cycle, by a series of successive ultrasound frames [2].

Based on these images, by post-processing, using a two-dimensional, even three-dimensional calculation algorithm, the dynamics of cardiac structures can be quantified. Therefore, due to its potential benefits in measuring left ventricular function, this new echocardiographic technique was used to analyze the relationship between non-alcoholic fatty liver disease and subclinical myocardial dysfunction of the left ventricle [3].

To the best of our knowledge, the technique has been used in obese adolescents with non-alcoholic fatty liver disease demonstrating that the global longitudinal systolic strain was significantly lower in obese individuals compared to the slim ones and that in patients associating obesity andnon-alcoholic fatty liver disease as opposed to those without this condition [5].

Karabay et al. showed, using the Speckle tracking technique, that patients with non-alcoholic fatty liver disease having no evidence of insulin resistance presented similar myocardial performance parameters in comparison with normal population [6].

In consequence, many more studies are needed to demonstrate the possible relationship between non-alcoholic fatty liver disease and subclinical myocardial dysfunction, especially in the firststages of this liver medical condition.

Aim

This study is aimed to asses the non-alcoholic fatty liver disease effets on myocardial function in asymptomatic patients by usingsensitive echocardiographic techniques.

Materials and Method

The population studied

We made an observational study which included 79 young patients aged 15-45 years, diagnosed with non-alcoholic fatty liver disease and a group of 80 healthy young people in the same age group.

In the group of patients with non-alcoholic liver disease, 35 patients had only liver damage, and 44 patients also had type 1 diabetes, in addition to liver damage.

The study was conducted at the Cardiology Centre of the Craiova County Emergency Clinical Hospital during 2016-2020.

The study was conducted taking into account the principles of the Helsinki Declaration and it was, also, approved by the Hospital Ethics Committee.

Each patient signed an informed consent after receiving information about the objectives of the study and non-invasive assessment methods.

Patients with a history of viral hepatitis and chronic liver disease (haemochromatosis, autoimmune hepatitis, Wilson's disease, liver disease caused by drugs or alcohol intake, cirrhosis of the liver) were not included in the study.

High blood pressure, sinus rhythm disorders (other than complex premature beats) and ischemic or valvular heart disease were other exclusion criteria.

Abdominal ultrasound was the method used to screen patients with suspected non-alcoholic fatty liver disease.

The characteristic imaging changes included unilobar or global hepatomegaly, with clear, regular contour, homogeneous structure, increased echogenicity, with posterior attenuation of the ultrasound signal, erasure of the vascular pattern and the appearance of the contrast difference between liver echogenicity and right kidney parenchyma.

Echocardiography

All patients underwent transthoracic echocardiographic examination, using the Speckle tracking technique, using a Vivid S6 echocardiograph (GE Vingmed Ultrasound, Horten, Norway). According to the laboratory's internal protocol, all echocardiographic examinations were stored, with the measurement of 3 cardiac cycles, in DICOM format. (Digital Imaging and Communications in Medicine) and post-processed offline using EchoPAC version 8.0 (GE Healthcare). Echocardiographic evaluation was performed after 5 minutes of rest. For the correct acquisition of the images, the patient was placed in left lateral decubitus. In order to synchronize the correct acquisition of the images together with the stages of the cardiac cycle, the ECG route was also recorded at the same time.

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The dimensions of the left ventricle together with interventricular septum, and also the posterior wall of the left ventricle were measured using M mode.

Ejection fraction, end-systolic volume together with the left ventricular end-diastolic volume were obtained by tracing the endocardium in the apical 2-chamber and the apical 3-chamber apical using the modified Simpson biplane method.

The measurement of the maximum systolic velocity S using the tissue Doppler examination allowed the evaluation of the left ventricle longitudinal systolic function determined by the contractility of the subendocardial fibers, oriented longitudinally from the base to the apex.

Global longitudinal (strain) myocardial deformity of the left ventricle was obtained by drawing the endocardial contour in all 3 apical incidents (4-,2-,3-chambers) on two-dimensional images (Figure 1).

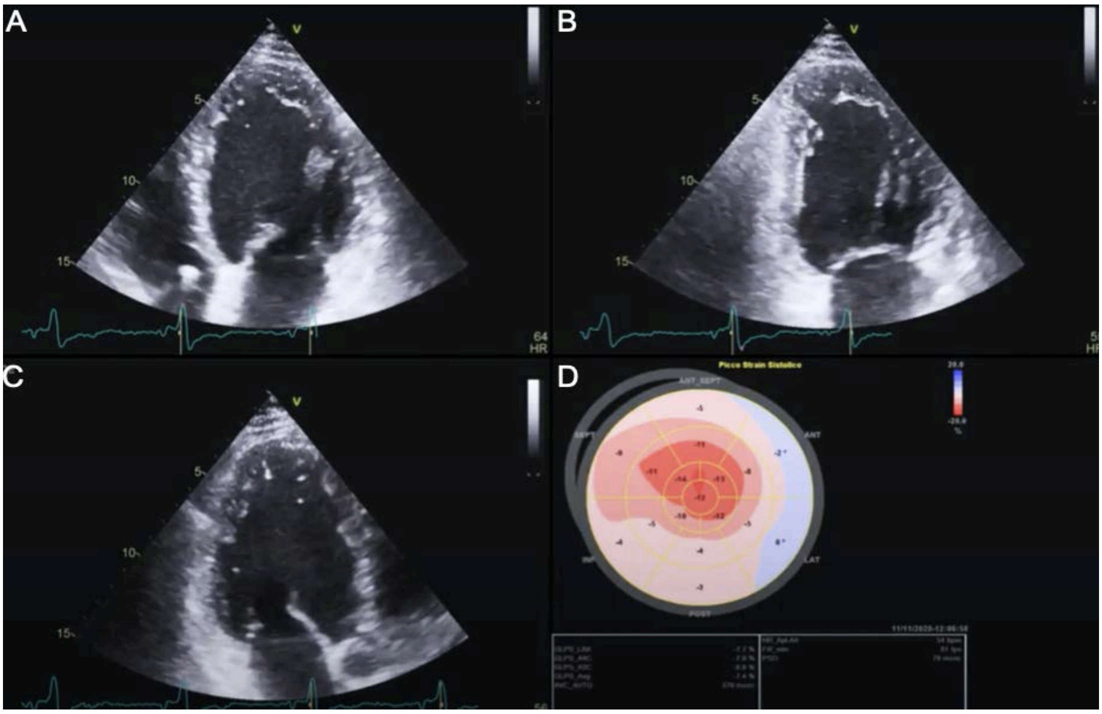

Figure 1. Speckle tracking echocardiography from personal archive. A-apical long-axis view 4 chambers. B-apical long-axis view 2 chambers. C-apical long-axis view 3 chambers. D-Bull's-eye plot.

End-systole was characterized by the closure of the aortic valve taking into account the pulsed Doppler image from the LV ejection tract and end-diastole as the peak of the R wave belonging tothe QRS complex visualized on the ECG route. The value of the global longitudinal deformation (GLS) was obtained offline by the automatic calculation by the software of the arithmetic mean of the segmental longitudinal strain, for analysis using a 17-segment model (six basal segments, six middle segments, four apical segments and a central segment illustrating the apex).

The analysis software allowed obtaining GLS values for both endocardium (GLS endo) and myocardium (GLS_mio) and epicardium (GLS_epi). GLS is expressed as a percentage, representing the total deformation during the cardiac cycle relative to the initial length. The final result was rendered in the form of a colour circle with six basal segments, six middle segments, four apical segments and one central segment illustrating the apex, called the bull's eye. Previous studies have shown that a cut-off value of the global longitudinal strain of-16 provides an important stratification of risk, while having a prognostic value [7].

The mechanical dispersion of the left ventricle represents the standard deviation of the times of reaching the maximum segmental systolic deformation, being an indicator of the myocardial heterogeneity. It was calculated by reporting the standard deviation of the time to reach the maximum longitudinal deformation for the 17 segments. Knowing that in subjects without cardiovascular disease, the apex has a counter-clockwise rotation, while base presents a clockwise rotation, we could first calculate the LV twist, represented by the difference between apical and basal rotation, for each moment of the cardiac cycle. Left ventricular torsion was obtained by relating the twist to the end-diastole diameter of the left ventricle, evaluated from the 4 C apical projection.

Circumferential deformation was obtained from short-axis parasternal incidences (including the following levels: mitral valve, papillary muscles and apical level), by manually tracing the contour of the endocardium. By convention, the circumferential strain has a negative value.

Statistical Analysis

All numerical data was represented as mean and standard deviation. Data was analyzed using Graph Pad software (version 9, La Jolla, CA, USA). For statistical analysis we used the student t test to compare the means of two data groups and the ANOVA test when we had to compare at least three data groups. In all cases the value of P was calculated, and we considered that there is a statistically significant difference between the means of the compared groups when it was less than 0.05.

Results

In this study, there were two groups of patients, namely the group of patients with non-alcoholic liver disease (n=79) of which 35 patients had only liver damage and 44 patients who had liver disease and diabetes (especially type 1 diabetes) and the control group represented by young people (n=80) with similar ages, healthy (Table 1).

Table 1. Clinical and demographic parameters of the population included in the study.

Variables	Non-alcoholic fatty liver disease (n=35)	Non-alcoholic fatty liver disease and Diabetes mellitus (n=44)	Control group (n=80)
Gender (Male/Female)	20/15	26/18	51/29
Age	38 ± 5	31 ± 8	29 ± 5
Body mass index (kg/m^2)	30 ± 3	27 ± 6	23 ± 3.9
Body surface area (m^2)	2.1 ± 0.1	1.8 ± 0.2	1.8 ± 0.2
Heart rate	77 ± 8	80 ± 10	80 ± 14
Systolic blood pressure	126 ± 8	126 ± 14	117 ± 7
Diastolic blood pressure	75 ± 9	80 ± 7	68 ± 5

We notice that the age of patients with hepatosteatosis was higher compared to the other two groups. Within the three groups, the patients with non-alcoholic fatty liver disease but also those with associated diabetes mellitus had a much higher weight and body mass index compared to the control group. Also, both patients with non-alcoholic fatty liver disease and those with associated diabetes had much higher blood pressure as opposed to the patients included in the control group. In contrast, no statistically significant differences in heart rate were recorded.

Table 2. The echocardiographic characteristics of the studied population.

Variables	Non-alcoholic fatty liver disease (n=35)	Non-alcoholic fatty liver disease and Diabetes mellitus (n=44)	Control group (n=80)
Left ventricle end-diastolic diameter (mm)	49.1 ± 5.1	44.5 ± 4.6	45.9 ± 4.7
Left ventricle end-systolic diameter (mm)	37.5 ± 4.5	30 ± 4.7	30.7 ± 4.4
Interventricular septum (mm)	11 ± 1.3	9.7 ± 1.9	8.2 ± 1.4
Left ventricle posterior wall (mm)	10.6 ± 1.3	9.2 ± 2.1	8.1 ± 1.3
Left ventricle mass (g/m^2)	94.52 ± 19.15	76.8 ± 23.7	67.04 ± 13.8
Left ventricle end-diastolic volume (ml/m^2)	52.1 ± 10.7	45.3 ± 10.4	52.5 ± 9.3
Left ventricle end-systolic volume (ml/m^2)	22.2 ± 5.4	18.1 ± 5.6	21.9 ± 4.6
LVEF (%)	57.2 ± 5.2	60.3 ± 7.2	58.2 ± 4.4
Septal S wave (cm/s)	7.9 ± 0.9	8.3 ± 1.4	9.8 ± 1.9
GLS endocardium (%)	-20.3 ± 2.4	-20.6 ± 2.6	-22 ± 2.4
GLS myocardium (%)	-17.7 ± 2	-18 ± 2.2	-19.2 ± 2.2
GLS epicardium (%)	-15.4 ± 1.8	-15.8 ± 2.1	-16.8 ± 2
Left ventricle torsion	10.4 ± 3.9	11.4 ± 5.9	13.8 ± 6.6
Left ventricle mechanical dispersion	39.99 ± 11.8	34.33 ± 11.8	28.44 ± 6.5
Basal circumferential strain	-19.7 ± 4.2	-19.1 ± 3.7	-20.4 ± 2.8
Mid circumferential strain	-23.5 ± 4.5	-22.3 ± 5.2	-21.2 ± 2.8
Apical circumferential strain	-27.7 ± 5.6	-27.4 ± 6.2	-28.2 ± 5.4

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Table 3. The value of p (ANOVA test).

Patients	Normal versus NAFLD	Normal versus NAFLD and diabetes	NAFLD versus NAFLD and diabetes
LVEDD	0,0349	0,4456	0,0013
LVESD	<0,0001	0,9636	<0,0001
IVS	<0,0001	0,0001	0,0358
LVPW	<0,0001	0,0178	0,0363
LV Mass	<0,0001	0,013	0,0009
LVEDV	>0,9999	<0,0001	0,0073
LVESV	>0.9999	0.0409	0.2536
LVEF	0,7374	0,1271	0,0993
S Wave	0,0089	0,0055	0,999
GLS endo	0,0288	0,006	>0,9999
GLS mio	0,0717	0,0486	0,9995
GLS epi	0,1327	0,121	0,9995
LV torsion	0,076	0,1006	0,8235
Mechanical dispersion	<0,0001	0,0025	0,069
Basal circumferential strain	0,768	0,123	0,8761
Mid circumferential strain	0,0951	0,3274	0,6735
Apical circumferential strain	0,9305	0,7457	0,9856

The cavitary dimensions (Figure 2A) of the left ventricle had higher values, statistically significant in the group of patients suffering from non-alcoholic liver disease versus the patients included in the control group. In contrast, the dimensions of the interventricular septum together with the dimensions of the posterior wall of the left ventricle had higher and statistically significant values both in the group of patients with non-alcoholic fatty liver disease and in the group of patients that also associated diabetes, when compared with the control group.

The mass of the left ventricle was calculated according to the Cube formula, and the latest recommendations set the values of $95g/m^2$ as upper limits for women, respectively $115g/m^2$ in the case of men. The results obtained showed a higher average and statistically significant value in the group of patients suffering from non-alcoholic liver disease and in the group of those associated with diabetes.

Regarding the volumes of the left ventricle (Figure 2B), there were no statistically significant differences between the group of patients suffering from non-alcoholic fatty liver disease and the control group, but the same was not found in the group of patients who also associated diabetes with liver disease, who had lower ventricular volumes.

All patients included in the study had a normal left ventricular ejection fraction but, when the longitudinal function of the left ventricle was assessed using the tissue Doppler technique (maximum systolic velocity S) statistically significant differences were found in both the group of patients with non-alcoholic fatty liver as well as in the group of patients associated with diabetes. Using speckle tracking echocardiography, we found a statistically significant decrease in global longitudinal strain in the endocardium, in the group of patients with non-alcoholic liver disease but also in the group of those with diabetes. The overall longitudinal strain at the myocardium was significantly reduced only in the group of patients suffering from non-alcoholic fatty liver disease and diabetes, while the overall longitudinal strain at the epicardium showed no changes in any of the groups studied (Figure 2C). Also, no changes were observed at the circumferential strain (Figure 2D).

In the conducted study we evaluated the torsion of the left ventricle as well as its mechanical dispersion. Analysis of left ventricular torsion for the studied patients did not bring statistically significant differences. The mean of studied parameter was slightly lower in the group of patients suffering from non-alcoholic fatty liver disease and in the group that associated diabetes compared to the control group, but without statistical significance. In the current paper, mechanical dispersion showed significant variations depending on the study group analyzed. Thus, the evaluation of the mechanical dispersion in the control group showed a lower mean of this parameter than the one determined in the patients in the patients' group, registering in this case a statistically significant difference.

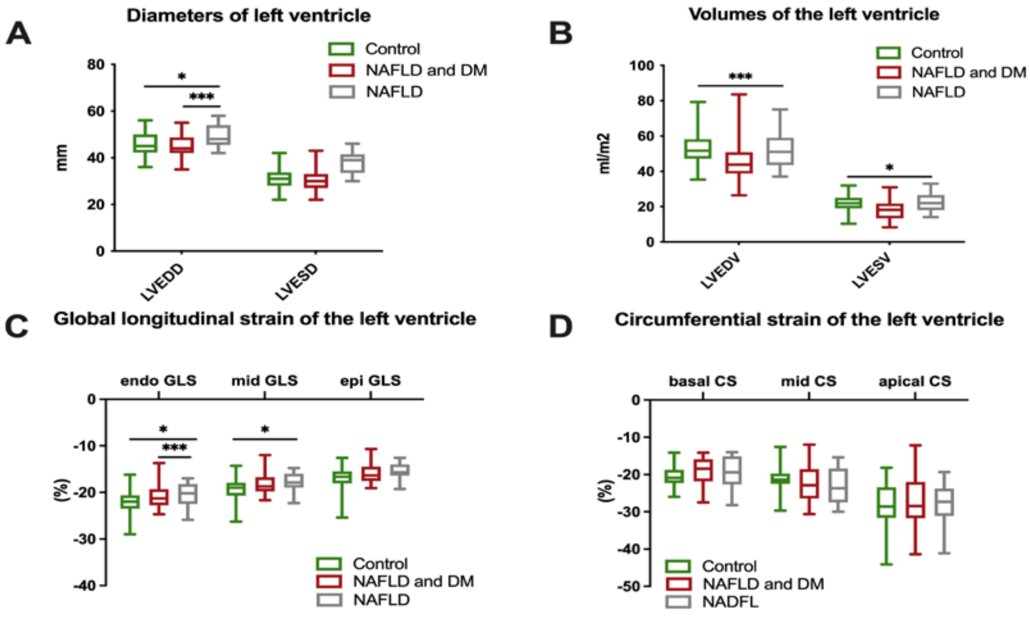

Figure 2. A-The diameters of left ventricle. B-The volumes of the left ventricle. C-Global longitudinal strain (GLS) of the left ventricle. D-Circumferential strain of the left ventricle. NAFDL=non-alcoholic fatty liver disease. DM= diabetes mellitus. CS=circumferential strain. LVEDD=left ventricle end-diastolic diameter. LVESD=left ventricle end-systolic diameter. LVEDV=left ventricle end-diastolic volume. LVESV=left ventricle end-systolic volume.

Discussions

In this study we investigated the presence of the left ventricle subclinical systolic dysfunction in patients suffering from non-alcoholic fatty liver disease, which cannot be detected using conventional echocardiography. In the current study, establishing the diagnosis of non-alcoholic fatty liver disease was based on ultrasound, but it is well known that abdominal ultrasound cannot distinguish between simple hepatic steatosis and steatohepatitis.

Although conventional echocardiography provides information on overall systolic function, by calculating the ejection fraction of the left ventricle, it has been shown that the change in this parameter is relatively late, emphasizing the need for early identification of subclinical myocardial dysfunction [7-25].

Conventional left ventricular echocardiographic parameters, such as end-diastolic and end-systolic diameter, showed significant variations only in the group of patients suffering from non-alcoholic liver disease and not in the group of patients associated with diabetes [8-10]. However, this result was to be expected given the younger age of the patients included in the non-alcoholic liver disease group with associated diabetes mellitus and the control group [11-15].

The relative thickness of the walls and the mass of the left ventricle showed significantly higher values in the group with non-alcoholic liver disease, but also in the group with diabetes associated with the control group, suggesting the appearance of left ventricular remodeling in these patients [16].

This remodeling may have an explanation in the presence of high blood pressure values in these patients. Previous studies have shown that non-alcoholic liver disease was linked with increased left ventricular mass and altered cardiac geometry [26-28].

Goland et al. [27] observed that normotensive patients, non-diabetics suffering from non-alcoholic fatty liver disease, in the absence of morbid obesity, have a slightly altered geometry, namely an increase in the interventricular septum, posterior wall and left ventricle mass. Sato et all also noticed in their study an increasing prevalence of ventricular hypertrophy among patients suffering from type 1 diabetes [29], with increased left ventricular mass beingan independent risk factor for several conditions including: sudden death, ventricular arrhythmias, and, nevertheless, heart failure [30,31].

Tissue Doppler echocardiography proved to bevaluable for evaluating the myocardial function in patients suffering from non-alcoholic liver disease. In the present study, the evaluation of systolic myocardial velocity (S’) derived from

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tissue Doppler revealed among patients with non-alcoholic liver disease but also in those with associated diabetes mellitus, the presence of longitudinal systolic dysfunction. The results of our study are in accordance with the results of other studies in young adult patients with non-alcoholic liver disease, which showed a decrease in longitudinal deformity of the left ventricle. Thus, Fotbolcu et al. [28] found a significant systolic dysfunction, detected by tissue Doppler method, in patients with non-alcoholic liver disease, non-diabetics, normotensive patients, although the ventricular size and ejection fraction did not change. Andersson et al. [32] showed, by using tissue Doppler imaging, that patients with diabetes mellitus without significant coronary heart disease had impaired longitudinal systolic function of the left ventricle. These observations suggest that early impairment of longitudinal left ventricular function could represent an early indicator of heart failure in these patients. Thus, tissue Doppler imaging appears to be a more sensitive method than determining the ejection fraction for the evaluation of early systolic dysfunction.

However, tissue Doppler imaging has technical limitations, the most important being the dependence on the interrogation angle. The development of another imaging technique, speckle tracking (STE) echocardiography, helps clinicians push these limits and its accuracy and clinical utility [22] have been reported in various pathologies such as myocardial ischemia, identification of chemotherapy-induced myocardial toxicity, evaluation of myocardial asynchrony, evaluation of right ventricular function [23-25].

Using speckle tracking echocardiography, we found that patients with non-alcoholic fatty liver disease have reduced longitudinal systolic function of the left ventricle, although the overall systolic function evaluated by the ejection fraction did not show significant changes between the studied groups. As it was expected, all patients demonstrated an endocardial-epicardial gradient, with the highest values of deformation in the endocardium, and the lowest in the epicardial layer. This information is in accordance with that existing in the literature [17,18].

The subendocardial fibers have a longitudinal orientation, and they are more vulnerable to pathological factors and the first that are affected incardiac pathologies. This may explain the reduction of global longitudinal strain in the endocardium in both patients with non-alcoholic liver disease and those with associated diabetes. It has also been observed that with the progression of the disease are affected myocardial together with subepicardial fibers, which determine circumferential and radial dysfunction, leading to a reduction in the ejection fraction of the left ventricle [17,19].

Global longitudinal myocardial strain showed a statistically significant reduction only in the group of patients suffering from non-alcoholic liver disease and diabetes, suggesting that the presence of diabetes may worsen the dysfunction of the left ventricularin patients suffering from non-alcoholic liver disease.

The absence of differences in the global longitudinal strain between the two subgroups (those with non-alcoholic liver disease and those with diabetes associated with non-alcoholic liver disease) can be explained by the presence of insulin resistance in patients included in the study, knowing that insulin resistance affects geometry and left ventricular function [20,21].

Evaluation of left ventricular torsion in patients associating non-alcoholic liver disease versus the control group did not show statistically significant results, which was similar to the few results in the literature [33].

The same result was recorded in patients with non-alcoholic liver disease and associated diabetes. A reduction in longitudinal and circumferential strain accompanied by an increase in torsion was already observedin patients with type 2 diabetes [33,34] compared to patients with non-alcoholic fatty liver disease, which is an indicator of the dominance of subepicardial fibers that exerts effects on the endocardium [35].

Torsion is a common characteristic of myocardial contraction and determines a counterclockwise twisting movement when the heart is analyzed from the peak to the base. Subepicardial fibers act on a larger radius, so, in contraction, they are dominant on the subendocardial fibers that try to counteract this twisting movement [35].

The endocardium dysfunction in type 2 diabetes characterized by a torsion increase can be caused by subendocardial fibrosis [35].

Left ventricle mechanical dispersion as measured by using speckle tracking echocardiography, as imagistic technique, is linked withventricular arrhythmias in somecardiomyopathies [36].

This represents an important information because of the need of risk markers above the ejection fraction in order to identify patients that are at risk of developing cardiac arrhythmias, some of them being life-threatening.

The evaluation of this parameter in our study brought importantnew data among patients suffering from non-alcoholic liver disease, but also those with associated diabetes. Reviewing the literature, a cohort study published by E.N.

Aagaard et al. [37] demonstrates that an increased value of LV mechanical dispersion is present in subjects with clinical conditions at risk of cardiovascular disease (obesity, hypertension, diabetes). This may suggest that people who are included into these categories are more likely to develop ventricular arrhythmic events. The data from our study could not be compared with data from the literature, because there are no studies assessing the mechanical dispersion in patients suffering from non-alcoholic liver disease, diabetes and young age.

Conclusions

Non-alcoholic fatty liver disease, diagnosed in asymptomatic young adults may be a risk factor for remodeling the left ventricle over time, being associated with subclinical myocardial dysfunction, regardless of the presence of other cardiovascular risk factors.

This study showed that the new imaging technique, speckle tracking, represents both an important and sensitive tool in order to detect early subclinical dysfunction of the left ventricle, being appliable for young patients diagnosed with non-alcoholic fatty liver disease.

Myocardial dysfunction of the left ventricle evaluated by the speckle tracking method begins in the subendocardial and myocardial layers, preserving the epicardial layer in early stages.

The presence of diabetes may aggravate left ventricular dysfunction in the cattegory of the patients suffering from non-alcoholic fatty liver disease, as evidenced by the reduction of the global longitudinal strain on the myocardium in this category of patients.

Young patients suffering from non-alcoholic fatty liver disease and those that also associat diabetes mellitus are at risk for life-threatening cardiac arrhythmias, supporting the hypotheses in the literature that mechanical dispersion can be considered a more accurate prognostic factor compared to the ejection fraction for identifying patients that are at risk.

Conflict of interests

None to declare.

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